FORMULATION DEVELOPMENT AND EVALUATION OF CAPSULE CONTAINING NICORANDIL LOADED OIL ENTRAPPED FLOATING ALGINATE BEADS FOR ANGINA PECTORIS

A Dissertation submitted to

THE TAMIL NADU Dr. M.G.R MEDICAL UNIVERSITY

CHENNAI – 600 032

in partial fulfilment of the requirements for the award of degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

submitted by

Register Number:261411268

under the guidance of

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COLLEGE OF PHARMACY

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CHENNAI – 600 003

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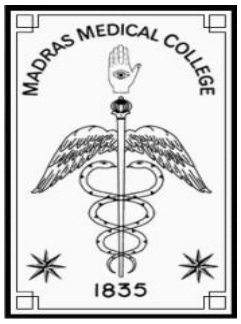

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This is to certify that the dissertation entitled **"FORMULATION DEVELOPMENT AND EVALUATION OF CAPSULE CONTAINING NICORANDIL LOADED OIL ENTRAPPED FLOATING ALGINATE BEADS FOR ANGINA PECTORIS"** submitted by the candidate with **Register No. 261411268** to The Tamil Nadu Dr. M.G.R. Medical University is evaluated.

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This is to certify that the dissertation entitled **"FORMULATION DEVELOPMENT AND EVALUATION OF COLON TARGETED COMPRESSION COATED TABLETS OF AMITRIPTYLINE HYDROCHLORIDE FOR IRRITABLE BOWEL SYNDROME"** submitted by the candidate with **Register No.261411270** in partial fulfillment of the requirements for the award of the degree of **MASTER OF PHARMACY** in **PHARMACEUTICS** by The Tamil Nadu Dr. M.G.R. Medical University is a bonafide work done by him during the academic year 2015-2016.

Place: Chennai – 03

Date :

(Dr. A. JERAD SURESH, M.Pharm., Ph.D., M.B.A)

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Place: Chennai – 03

Date:

[Prof. K.ELANGO, M.Pharm., (Ph.D.),]

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ABBREVATIONS

GRDDS	Gastro Retentive Drug Delivery System
GIT	Gastro Intestinal Tract
GRT	Gastric Retention Time
GET	Gastric Emptying Time
FDDS	Floating Drug Delivery System
CRGRDF	Controlled Release Gastro Retentive Dosage Form
FAB	Floating Alginate Beads
CDDS	Controlled Drug Delivery System
KSI	Kiloponds per Square Inch
HPMC	Hydroxy Propyl Methyl Cellulose
CMC	Carboxy Methyl Cellulose
LV	Low Viscosity
HBS	Hydro-dynamically Balanced System
IGM	Ionotropic Gelation Method
NSAID	Non Steroidal Anti- Inflammatory Drug
CHD	Coronary Heart Disease
CAD	Coronary Artery Disease
ACS	Acute Coronary Syndrome
MI	Myocardial Infarction
CAC	Coronary Artery Calcium
ECG	Electrocardiogram
CT	Computed Tomography

MDCT	Multi Detector Computed Tomography
EBCT	Electron-Beam Computed Tomography
ACE	Angiotensin Converting Enzymes
CABG	Coronary Artery Bypass Grafting
DMSO	Dimethyl Sulfoxide
ATP	Adenosine Tri Phosphate
GMP	Guanosine Mono Phosphate
FTIR	Fourier Transform Infrared
DL	Drug Loading
EE	Entrapment Efficiency
USP	United States Pharmacopeia
BP	British Pharmacopeia
USPNF	United States Pharmacopeia and National Formulary
SEM	Scanning Electron Microscope
RPM	Revolution Per Minute
HCl	Hydrochloric acid
mmHg	Mercuric millimeter
mg	Milligram
mL	Milliliter
µg	Microgram
nm	Nanometer
%	Percentage

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ORAL DRUG DELIVERY SYSTEMS

Oral drug delivery is the most widely used route of administration among all the routes that have been developed for systemic delivery of drugs. Despite tremendous advancement in drug delivery, oral route is considered most convenient , uncomplicated, and safe due to its ease of administration, patient acceptance and cost effective manufacturing process. Most of the pharmaceutical products designed for oral delivery are immediate release types which are designed for rapid absorption of drug.[1]

CAPSULES[2]

Capsules are solid dosage forms in which the medication is contained within gelatin shells. The medication may be a powder, a liquid or a semisolid mass.

Advantages

- ✓ Neat and elegant in appearance.
- ✓ Enclosing the medication within capsule shells provides atasteless, odourless means of administering medication.
- ✓ The ready solubility of gelatin at gastric pH provides rapidrelease of medication in the stomach.

Types of capsules

- **Hard gelatin capsules**
  - ✓ It consists of two pieces in the formof cylinders: the shorter piece “cap” andthe longer piece “body”.
  - ✓ The shells consist largely of gelatin,sugar and water.
  - ✓ Size of capsules:

Size	000	00	0	1	2	3	4	5
Volume	1.37	0.95	0.68	0.50	0.37	0.30	0.21	0.13

Table 1: Size of capsule shells

- **Soft gelatin capsules**
  - ✓ It consist of a continuous gelatin shell surrounding aliquid core.
  - ✓ It is formed, filled, and sealed in one operation.
  - ✓ It is oblong, spherical, elliptical in shape.

- ✓ The capsule shell consists of gelatin, water andplasticizer.
- ✓ Plasticizer makes the shell elastic.e.g. glycerol, sorbitol and propylene glycol.

CONTROLLED RELEASE DRUG DELIVERY SYSTEMS (CDDS)[3]

Controlled release drug delivery system was designed to deliver for a prolongedperiod. Safe and effective blood levels are maintained for longer period as the system continues to deliver the drug. CDDS usually results in constant blood levels of the drug as compared to the uncontrolled fluctuations observed when multiple doses of quick releasing conventional dosage forms are administered to a patient.

The driving force behind the development of sustained release formulations is the wish to extend the effective half-life of the drug and hence reduce dosing frequency or to minimize the differences between peak and trough plasma levels.

Advantages

Controlled release products offer many potential benefits over conventional dosage formulations , they are

- ✓ Avoid patient compliance
- ✓ Less total drug is used
- ✓ Minimize local side effects and systemic side effects
- ✓ Obtain less reduction in drug activity in chronic use
- ✓ Minimize the drug accumulation with chronic dosing
- ✓ Improve efficiency in treatment and cures the condition more promptly
- ✓ Bioavailability of some drugs is improved
- ✓ Make use of special effects, e.g., sustained release of aspirin for morning relief of arthritis by dosing before bed.

Disadvantages

- ✓ Decreased systemic availability in comparison to immediate release formulation or conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site specific absorption on, pH dependent stability,etc.
- ✓ Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.

- ✓ Reduced potential for dosage adjustment of drugs normally administered in varying strengths.
- ✓ Stability problems.

GASTRORETENTIVE DRUG DELIVERY SYSTEMS[1,4]

Dosage form with a prolonged gastric residence and controlled drug delivery are called as GRDDS. Oral controlled release dosage forms are developed due to their therapeutic advantages such as patient compliance, ease of administration and flexibility in formulation. However this approach has several physiological difficulties such as inability to locate the dosage form at the desired region of the gastrointestinal tract (GIT) due to variable gastric emptying time. The gastric emptying time in human normally ranges from 2-3 hours through which the major absorption zone (stomach and upper part of intestine) passes through that so the dosage form can result in incomplete drug absorption from the delivery system and leading to reduced efficacy of the administered dose. Therefore, the control of placement of a drug delivery system in a specific region of the GIT offers greater advantage. The drugs characterized by a narrow absorption window in the GIT or drugs with a stability problem in the intestine can be benefitted by this approach. These have led to the development of a unique oral controlled release dosage form with gastro retentive properties. After oral administration, such a dosage form would be retained in the stomach and release the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper GIT.

ANATOMICAL AND PHYSIOLOGICAL ASPECTS OF THE STOMACH[4,5]

A basic understanding of the anatomical and physiological aspects of the stomach isneeded for a pharmaceutical formulator to develop successful gastro retentive formulation. The main function of the stomach is to process and transport food. It serves as a short-term storage reservoir, allowing a rather large meal to be consumed quickly.Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions.

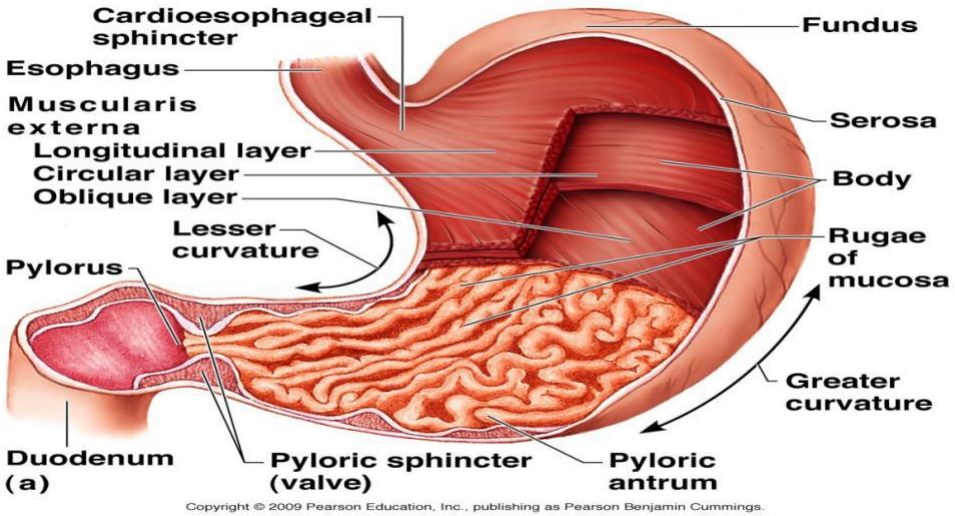


Fig. 1: Anatomical representation of the stomach

Stomach Physiology[5,6]

The stomach is an expanded section of the digestive tube between the oesophagus and small intestine. The wall of the stomach is structurally similar to the other parts of the digestive tube, with the exception that stomach has an extra, oblique layer of smooth muscle inside the circular layer, which aids in the performance of complex grinding motions. In the empty state, the stomach is contracted and its mucosa and sub mucosa are thrown up into distinct folds called rugae.

The four major types of secretary epithelial cells that cover the surface of the stomach and extend down into gastric pits and glands. They are

- ✓ **Mucous cells** secrete alkaline mucus that protects the epithelium against shear stress and acid.
- ✓ **Parietal cells** secrete hydrochloric acid.
- ✓ **Chief cells** secrete pepsin, a proteolytic enzyme.
- ✓ **G cells** secrete the hormone gastrin. The contraction of gastric smooth muscle serves two basic functions:
    - Ingested food is crushed, ground, mixed and liquefying to form Chyme.
    - Chyme is forced through the pyloric canal into the small intestine, a process called gastric emptying.

Gastric emptying[5,6]

Gastric emptying occurs during fasting as well as fed states. Thepattern of motility is however distinct in the 2 states.During the fasting state, an interdigestive series of electrical events take place,which cycle both through stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4phases

1. Phase I (Basal phase) lasts from 30 to 60 minutes with rarecontractions.

2. Phase II (Preburst phase) lasts for 20 to 40 minutes withintermittent action potential and contractions. As the phaseprogresses the intensity and frequency also increases gradually.

3. Phase III (burst phase) lasts for 10 to 20 minutes. It includesintense and regular contractions for short period. It is due tothis wave that all the undigested material is swept out of thestomach down to the small intestine. It is also known as thehousekeeper wave.

4. Phase IV lasts for 0 to 5 minutes and occurs between phases IIIand I of 2 consecutive Cycles.

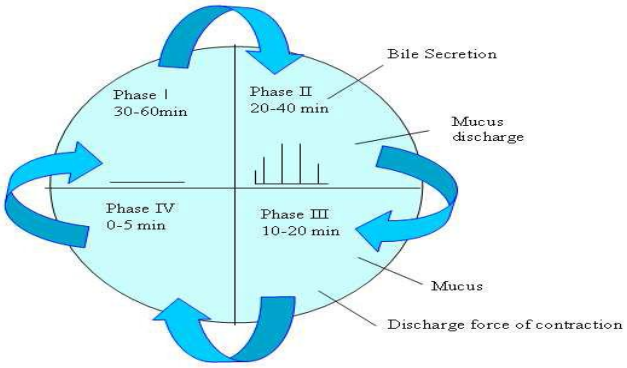


Fig.2: Motility pattern in GIT

FACTORS AFFECTING GASTRIC RESIDENCE TIME OF FDDS[4,7,8]

The stomach anatomy and physiology contain parameters to be considered in the development ofgastroretentive dosage forms. To pass through the pyloric valve in to the small intestine the particle size should be in the range of 1 to 2 mm. The most important parameters controlling the gastric retention time (GRT) of oral dosage forms include:

1. Density of dosage forms

Density of the dosage form should be less than the gastric contents(1.004gm/ml).

2. Shape and size of the dosage forms

Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT competed to with those with a diameter of 9.9 mm. The dosage form with a shape tetrahedron and ring shapedevices with a flexural modulus of 48 and 22.5 kiloponds per Square inch (KSI) is reported to have better GITretention 90 to 100 % retention at 24 hours compared with other shapes.

3. Viscosity grade of polymer

Drug release and floating properties of FDDS are greatly affected byviscosity of polymers and their interaction. Low viscosity polymers(e.g., HPMC K100 LV) were found to be more beneficial than highviscosity polymers (e.g., HPMC K4M) in improving floatingproperties. In addition, a decrease in the release rate was observedwith an increase in polymer viscosity.

3. Food intake and its nature

Food intake, viscosity and volume of food, caloric value and frequency of feeding have a profound effect on the gastric retention of dosage forms. The presence or absence of food in the gastrointestinal tract (GIT) influences the gastric retention time (GRT) of the dosage form. Usually the presence of food in the gastrointestinal tract (GIT) improves the gastric retention time (GRT) of the dosage form and thus, the drugsabsorption increases by allowing its stay at the absorption site for a longer period. Again, increase in acidity and caloric value shows down gastric emptying time (GET), which can improve the gastric retention of dosage forms.

4. Concomitant intake of drugs

Drugs such as prokinetic agents (e.g., metoclopramide and cisapride), anti Cholinergics (e.g., atropine or propantheline),opiates (e.g., codeine) may affect the performance of FDDS. The coadministration of GI-motility decreasing drugs can increase gastric emptying time.

4. Effect of gender, posture and age

Gender

Women have slower gastric emptying time than do men. Mean ambulatory GRT in meals (3.4±0.4 hours) is less compared with their age and race-matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.

Age

Low gastric emptying time is observed in elderly than do in younger subjects. Intrasubject and intersubject variations also are observed in gastric and intestinal transit time. Elderly people, especially those over 70 years have a significantly longer GRT.

Posture

i) Upright position

An upright position protects floating forms against postprandial emptying because the floating form remains above the gastric contents irrespective of its size. Floating dosage forms show prolonged and more reproducible GRTs while the conventional dosage form sink to the lower part of the distal stomach from where they are expelled through the pylorus byantral peristaltic movements.

ii) Supine position

This position offers no reliable protection against early and erratic emptying. In supine subjects large dosage forms (both conventional and floating) experience prolonged retention. The gastric retention of floating forms appear to remain buoyant anywhere between the lesser and greater curvature of the stomach. On moving distally, these units may be swept away by the peristaltic movements that propel the gastric contents towards the pylorus, leading to significant reduction in GRT compared with upright subjects.

SUITABLE DRUG CANDIDATES FOR GASTRORETENTION[6]

In general, appropriate candidates for CRGRDF are molecules that have poor colonic absorption but arecharacterized by better absorption properties at the upper parts of the GIT:

• Narrow absorption window in GI tract, e.g., Riboflavin and Levodopa

• Primarily absorbed from stomach and upper part of GI tract, e.g., Calcium supplements, Chlordiazepoxide and Cinnarazine

• Drugs that act locally in the stomach, e.g., Antacids and Misoprostol

• Drugs that degrade in the colon, e.g., Ranitidine HCl and Metronidazole

• Drugs that disturb normal colonic bacteria e.g., Amoxicillin trihydrate

APPROACHES TO GASTRORETENTION[9,10]

Several techniques are reported in the literature to increase thegastric retention of drugs.

1) Highdensitysystems

These systems, which have a density of ~3g/cm3, are retained in the rugae of stomach and capable of withstanding its peristalticmovements.The only major drawback with these systems is that it is technicallydifficult to manufacture them with a large amount of drug (>50%)and achieve required density of 2.4-2.8g/cm3. Diluents such as barium sulphate (density= 4.9), zinc oxide, titanium oxide, and ironpowder must be used to manufacture such high-density formulation.

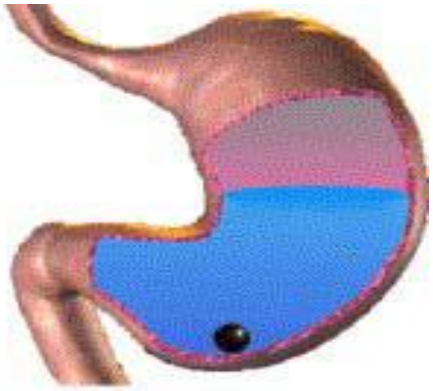


Fig.3:High density systems

2) Swelling and expanding systems

These systems are also called as "Plug type system", since theyexhibit tendency to remain logged in the pyloric sphincters. These polymeric matrices remain in the gastric cavity for several hourseven in fed state.

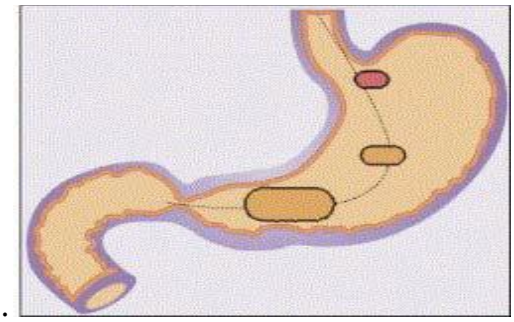


Fig.4: Swellable tablet in stomach

By the selection of polymer with proper molecular weight andswelling properties controlled and sustained drug release can beachieved. Upon coming in contact with gastric fluid, the polymerimbibes water and swells. The extensive swelling of these polymersis a result of the presence of physical-chemical cross links in thehydrophilic polymer network. These cross link prevents thedissolution of polymer and thus maintain the physical integrity ofthe dosage form. A high degree of cross linking retards the swellingability of the system and maintains its physical integrity forprolonged period. On the other hand, a low degree of cross linkingresults in extensive swelling followed by the rapid dissolution ofpolymer.

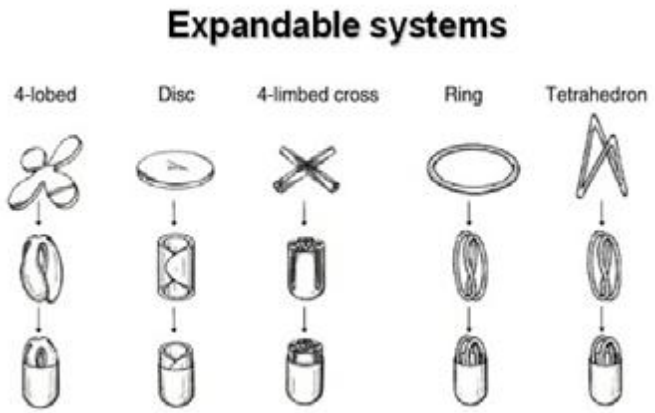


Fig.5: Different geometric forms of unfoldable systems

3) Incorporating delaying excipients:

Another delayed gastric emptying approach of interest include feeding of digestible polymers or fatty acid salts that charges themotility pattern, of the stomach to a fed stage thereby decreasing thegastric emptying rate and permitting considerable

prolongation ofthe drug release. Prolongation of GRT of drug delivery systemconsists of incorporating delaying excipients like trietanolamine myristate in a delivery system.

4) Modified systems:

Systems with non disintegrating geometric shape molded from silastic elastomers or extruded from polyethylene blends, whichextend the GRT depending on size, shape and flexural modules ofdrug delivery device.

5) Mucoadhesive & Bioadhesive systems

Bioadhesive drug delivery systems are used to localize a deliverydevice within the lumen to enhance the drug absorption in a site specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach.Some of the most promising excipients that have been usedcommonly in these systems include polycarbophil, carbopol, lectins,chitosan, CMC and gliadin, etc.

6) Floating systems

Floating drug delivery systems (FDDS) have a bulk density less thangastric fluids and so remain buoyant in the stomach withoutaffecting the gastric emptying rate for a prolonged period of time.While the system is floating on the gastric contents, the drug isreleased slowly at the desired rate from the system. After release ofdrug, the residual system is emptied from the stomach. Floatationof a drug delivery system in the stomach can be achieved byincorporating floating chamber filled with vacuum, air, or inert gas.

MECHANISM OF FLOATING SYSTEMS[11]

Floating drug delivery systems (FDDS) have bulk density lesser than gastric fluid, sothey remain buoyant in the stomach without affecting the gastric emptying rate for aprolonged period of time, while the system is floating on the gastric contents the drugreleased slowly at the desired rate from the system. However, besides aminimal gastric content needed to allow the proper achievement of the buoyancy retentionprinciple, a minimal level of floating force (F) is also required to keep the dosage formreliably buoyant on the surface of the meal. To measure the floating force kinetics, a novelapparatus for determination of resultant weight has been reported. The apparatus operates bymeasuring continuously the force equivalent to F (as function of time) that is required tomaintain the submerged object. The object floats better if F is on

the higher positive side. This apparatus helps in optimizing FDDS with respect to stability and durability of floating force proceed in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations.

$$F = F_{Buoyancy} - F_{Gravity} = (Df - Ds)\, gv$$

Where,

F = total vertical force;

Df = fluid density;

Ds =object density

V = volume

g =acceleration due to gravity

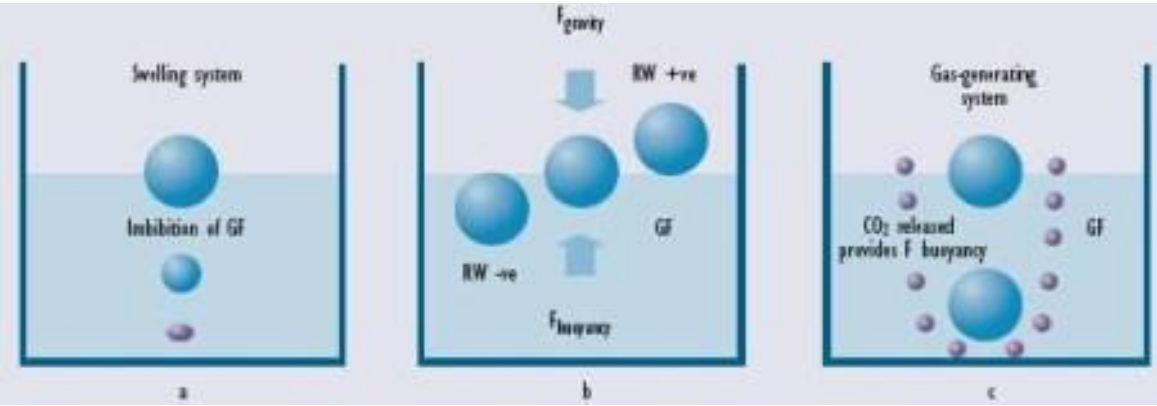


Fig.6: Mechanism of floating systems

ADVANTAGES OF FLOATING DOSAGE FORM[9]

(1) These systems are particularly advantageous for drugs that arespecifically absorbed from stomach or the proximal part of the smallintestine, e.g., riboflavin and furosemide.

(2) The fluctuations in plasma drug concentration are minimized, and concentration-dependent adverse effects that are associatedwith peak concentrations can be prevented. This feature is of specialimportance for drugs with a narrow therapeutic index.

(3) The efficacy of the medicaments administered utilizing thesustained release principle of floating formulation has been found tobe independent of the site of particular medicaments.

(4) Complete absorption of the drug from the floating dosage form isexpected even at the alkaline pH of the intestine. The dissolution ofthe drug in gastric fluid occurs and then the

dissolved drug isavailable for absorption in the small intestine after emptying of thestomach contents.

(5) Poor absorption is expected when there is vigorous intestinalmovement and a shorted transit time as might occur in certain typeof diarrhea. Under such circumstances it may be advantageous tokeep the drug in floating condition in stomach to get a relatively better response.

(6) Drugs that have poor bioavailability because of site-specificabsorption from the upper part of the gastrointestinal tract arepotential candidates to be formulated as floating drug deliverysystems, thereby maximizing their absorption. A significantincrease in the bioavailability of floating dosage forms (42.9%)could be achieved as compared with commercially available LASIX tablets (33.4%) and enteric-coated LASIX-long product(29.5%).

LIMITATIONS OF FLOATING DRUG DELIVERY SYSTEMS[9]

(1) A high level of fluid in the stomach is required for drug deliveryto float and work efficiently.

(2) Drugs which have stability and solubility problems in GIT arenot suitable candidates for these types of systems.

(3) Drugs such as Nifedipine, which under goes first passmetabolism may not be desirable for the preparation of these types of systems.

(4) Drugs which are irritant to gastric mucosa are also notdesirable.

(5) The drug substances that are unstable in the acidicenvironment of the stomach are not suitable candidates to be incorporated in the systems incorporated in the systems.

CLASSIFICATION OF FDDS BASED ON MECHANISM OFBUOYANCY[9]

A) Single unit

Single unit dosage forms are easiest to develop but suffers from therisk of losing their effects too early due to their all-or-none emptyingfrom the stomach and, thus they may cause high variability inbioavailability and local irritation due to large amount of drugdelivered at a particular site of the gastro intestinal tract.

Non-effervescentsystems

One or more gel forming, highly swellable, cellulosic hydrocolloids(e.g. hydroxyl ethyl cellulose, hydroxyl propyl cellulose,hydroxyl propyl methyl cellulose [HPMC] and sodium carboxy methylcellulose), polysaccharides, or matrix forming polymers(e.g.,polycarbophil, polyacrylates, and polystyrene) are incorporated inhigh level (20-75% w/w) to tablets or capsules.For the preparation of these types of systems, the drug and the gelforminghydrocolloid are mixed thoroughly. After oraladministration this dosage form swells in contact with gastric fluidsand attains a bulk density of < 1. The air entrapped within theswollen matrix imparts buoyancy to the dosage form. The so formedswollen gel-like structure acts as a reservoir and allows sustainedrelease of drug through the gelatinous mass.

Effervescent systems or gas generating systems

These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan andvarious effervescent compounds, e.g. sodium bicarbonate, tartaricacid, and citric acid. They are formulated in such a way that when incontact with the acidic gastric contents, CO2 is liberated and getsentrapped in swollen hydrocolloids, which provides buoyancy to thedosage forms. The optimal stoichiometric ratio of citric acid andsodium bicarbonate for gas generation is reported to be 0.76:1.

B) Raft Forming systems

Raft Forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and other disorders. The mechanism involved in the raft formation includes the formation of a viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. The raft swells in the gastric fluid because of the low bulk density created by the formation of CO_2. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of $CO_2$to make the system less dense and able to float on the gastric fluids. It is used for the treatment of Helicobacter pylori infections in the GIT.

Fig.7: Raft forming system

C) Multiple unit

Single unit formulations are associated with problems such assticking together or being obstructed in gastrointestinal tract, whichmay have a potential danger of producing irritation. Multiple unitsystems **avoid the 'all-or-none' gastric emptying nature of singleunitsystems.** It reduces the intersubject variability in absorption and the probability for dose dumping is lower.

Effervescent systems

A multiple unit system comprises of calcium alginate core and calcium alginate/PVA membrane, both separated by an air compartment was prepared. In presence of water, the PVA leachesout and increases the membrane permeability, maintaining the integrity of the air compartment. Increase in molecular weight and concentration of PVA, resulted in enhancement of the floatingproperties of the system. Freeze-drying technique is also reported for the preparation of floating calcium alginate beads. Sodium alginate solution is added drop wise into the aqueous solution of calcium chloride, causing the instant gelation of the droplet surface, due to the formation of calcium alginate. The obtained beads are freeze-dried resulting in a porous structure, which aid in floating.

Non-effervescent systems[11]

The Non-effervescent FDDS is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescentFDDS are gel forming or highly swellable cellulose type hydrocolloids, hydrophilic gums, polysaccharides and matrix forming materials such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymers such as

Chitosan and Carbopol.

The various types of this system are as:

1. Colloidal Gel Barrier Systems

Hydro-dynamically balanced system (HBS) of this type contains drug with gel forming or swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers. They help in prolonging the GI residence time and maximize drug reaching its absorption site in the solution form ready for absorption. These systems incorporate high levels (20 to 75 % w/w) of one or more gel forming highly swellable cellulose type hydrocolloids e.g. Hydroxy ethyl cellulose, Hydroxy propyl cellulose, Hydroxy propyl methyl cellulose, Sodium carboxy methyl cellulose incorporated either in tablets or capsules.

2. Micro porous compartment system

This technology is comprised of encapsulation of a drug reservoir inside a micro porous compartment with pores along its top and bottom surfaces. The peripheral walls of thedrug reservoir compartment are completely sealed to prevent any direct contact of gastricmucosal surface with undissolved drug. In stomach, the floatation chamber containingentrapped air causes the delivery system to float over the gastric contents. Gastric fluid entersthrough the pores, dissolves the drug and carries the dissolved drug for continuous transportacross the Intestine for absorption.

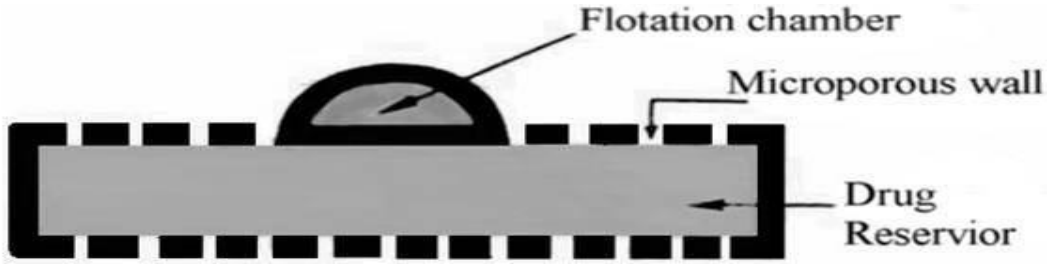


Fig.8: Micro porous intra-gastric floating drug delivery device

3. Hollow Microspheres

Hollow microspheres (Microballoons), loaded with drug in their outer polymer shellsare prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethanesolution of the drug and an enteric acrylic polymer is poured into an agitated aqueoussolution of PVA that is thermally controlled at 40 °C. The gas phase

generated in dispersedpolymer droplet by evaporation of dichloromethane forms an internal cavity in microsphereof polymer with drug. The Microballoons float continuously over the surface of acidicdissolution media containing surfactant for more than 12 hours.

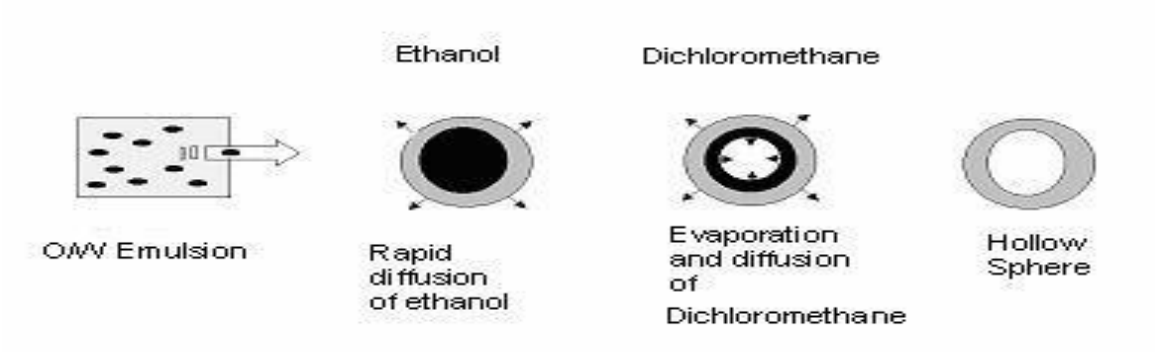


Fig.9: Mechanism of micro balloon formation by emulsion-solvent diffusion Method

4. Alginate Beads

Multi-unit floating dosage forms were developed from freeze dried calcium alginate.Spherical beads of approximately 2.5 mm diameter can be prepared by dropping sodiumalginate solution into aqueous solution of calcium chloride, causing precipitation of calciumalginate leading to formation of porous system, which can maintain a floating force for over12 hours. When compared with solid beads, which gave a short residence time of 1 hour, these floating beads gave a prolonged residence time of more than 5.5 hours.

Fig.10:Alginate beads

METHOD OF PREPARATION:

Alginate beads can be prepared by two methods. They are

- Ionotropic gelation method
- Emulsion gelation method

Ionotropic gelation method[12]

Alginate beads can also be prepared by Ionotropic gelation method. IGM is based on the ability of polyelectrolytes to cross link in the presence of counter ions to form hydrogel beads also called as gelispheres. Gelispheres are spherical crosslinked hydrophilic polymeric entity capable of extensive gelation and swelling in simulated biological fluids and the release of drug through it controlled by polymer relaxation. The hydrogel beads are produced by dropping a drug-loaded polymeric solution into the aqueous solution of polyvalent cations. The cations diffuses into the drug-loaded polymeric drops, forming a three dimensional lattice of ionically crosslinked moiety. Biomolecules can also be loaded into these gelispheres under mild conditions to retain their three dimensional structure

Polyelectrolyte solution

[Sodium Alginate (-)/Gellan gum (-)/CMC (-)/Pectin (-)/ Chitosan (+) + Drug]

↓

Added drop wise under magnetic stirring by needle

↓

Counter ion solution

[Calcium chloride solution (+)/Sodium tripolyphosphate (-)]

↓

Gelispheres

Emulsion gelation method:

Oil entrapped Floating Alginate beads is prepared by Emulsion Gelation method. In this method, Sodium alginate solution is prepared by dissolving sodium alginate

indistilled demineralized water with agitation. Oil phase in the concentration from 10% to 30% v/v is added with high shear mixing. The dug to be formulated is then dispersed in the formed emulsion. This mixture was extruded, using syringe of required needle gauge size into calcium chloride solution(1-5%w/v). The gel beads were allowed to stand in solution for some time with mild stirring (curing time) before being separated and dried.

EMULSION GELATION METHOD

Sodium Alginate + Distilled water

↓(Dissolve)

Add Oil phase

↓(High shear mixing)

Formation of O/W Emulsion

↓

Drug is Dispersed

↓

Extruded into Calcium chloride solution

↓

Gel beads allowed to stand in solution(curing time)

↓

Collected, Washed and Dried

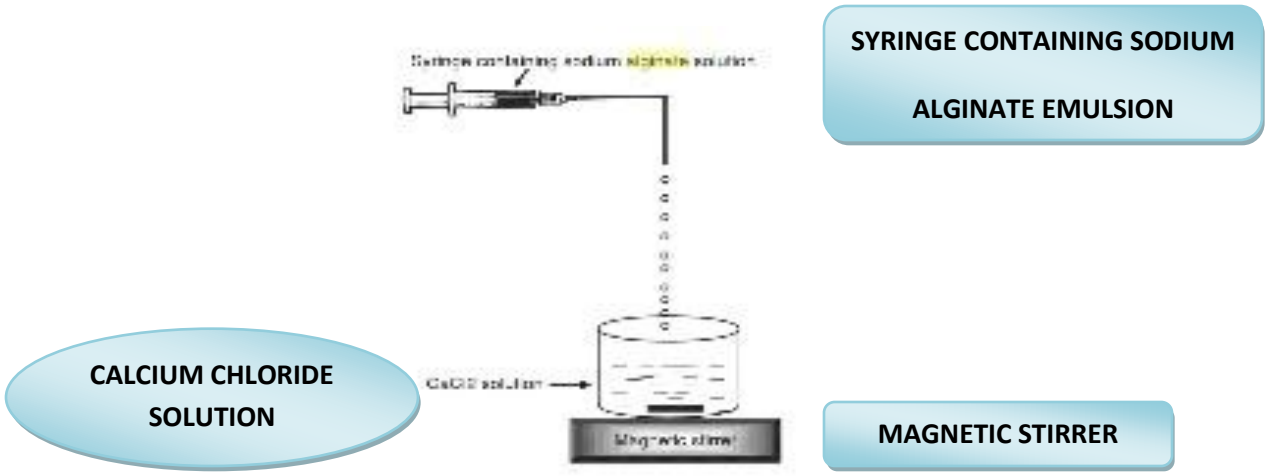


Fig.11: Experimental setup of Preparation of Alginate beads

FUTURE SCOPE OF FLOATING MULTIPLE UNIT DRUG DELIVERY SYSTEM[13]

Floating multiparticles can greatly improve the pharmacotherapy of the stomach through local drug release, used to eradicate Helicobacter pylori from the sub-mucosal tissue of the stomach most effectively and making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis. This system allows administration of non-systemic, controlled release antacid formulation containing calcium carbonate and also locally acting anti-ulcer drug (such as Lansoprazole) in stomach. Byoyant micro particles are considered as a beneficial strategy for the treatment of gastric and duodenal cancers.

Floating multiparticles of NSAID's are very effective for reducing their major side effect, gastric irritation as well as for controlled release.They may be used as a carrier for the drugs having narrow absorption windows, for example antiviral, antifungal and antibiotics.In addition, by continually supplying the drug to its most efficient site of absorption n, the dosage form may allow for more effective oral use of peptide and protein drugs such as calcitonin, erythropitin, vasopressin low molecular weight heparin.

Table2:List of Floating multiparticulate Marketed prepatrations

S.No.	BRAND NAME	DRUG(DOSE)	COMPANY	DOSAGE FORM
1.	Conviron	Ferrous sulfate	Ranbaxy,India	Colloidal gel forming FDDS
2.	Cytotec	Misopristol (100/200mcg)	Pharmacia	Bilayer floating capsule
3.	Topalkan	Al-Mg Antacid	Pierre Fabre Drug, France	Floating liquid alginate preparation
4.	MODAPAR	Levodopa(100mcg) Benserzide(25mcg)	Roche products, USA	Floating CR capsules
5.	Liquid Gavison	AluminiumHydroxide (95 mg) Magnesium carbonate(358mg)	GSK, India	Effervescent floating liquid alginate preparation
6.	Valrelease	Diazepam(15mg)	Hoffmann-LaRoche, USA	Floating capsules

1. **JadupatiMalakar*et al.*[14]** formulated and evaluated *(in-vitro* and *in-vivo*) floating capsules containing Alginate based beads of Salbutamol sulfate. Salbutamol sulfate-loaded oil-entrapped beads were prepared and capsulated within hard gelatin capsules (size 1). The effects of HPMCK4M and potato starch weight masses on drug encapsulation efficiency (DEE) of beads and cumulative drug release at 10 h (R10 h) from capsules was analyzed by 32factorial design. The optimization results indicate increasing of DEE in the oil-entrapped beads and decreasing R10 h from capsules with increment of HPMC K4M and potato starch weight masses. These capsules showed floatation over 6 h and sustained drug release over10 h in gastric pH (1.2). In vivo X-ray imaging study of optimized floating capsules in rabbits showed stomach-specific gastro retention over a prolonged period.

2. **Durgajaiswal*et al.*[15]**formulated and evaluated oil entrapped floating alginate beads of ranitidine hydrochloride.The objective of this investigation was to develop a multi-unit gastroretentive sustained release dosage form of a water soluble drug, Ranitidine hydrochloride. A new emulsion gelation technique was used to prepare emulsion gel beads using sodium alginate and pectin as polymers and their sustaining abilities were studied. The effects of factors like concentration of oil, curing time, drug: polymer ratio, alginate: pectin ratio and curing agent on drug entrapment efficiency, floating lag time, morphology and drug release were studied.The results show that these beads can entrap even a water soluble drug as Ranitidine hydrochloride in sufficient amount and also can successfully deliver the drug in stomach for a prolong duration of time without using any organic solvent and any time consuming step in the preparation.

3. **Mowafaq M *et al.*[16]**formulated and evaluated Trimetazidinedihydrochloride Floating beads. The study's objective was to develop gastro-retentivefloating beads that control the drug release which is freely soluble in water and suffers from rapid absorption and relatively short plasma half- life (6.0±1.4). By emulsion gelation method, trimetazidine floating beads were prepared using

sodium alginate,HPMC and peppermint oil. The effect of sodium alginate concentrations (2,3 and 4%w/v), peppermint oil percentage (15,20 and 25%v/v) and HPMC type on floating properties besides in-vitro drug release from the beads were studied. According to similarity factor, formulas which contain 2%w/v sodium alginate, 20%v/v oil and HPMC (15 000 centipoises) were the best formulas that showed higher similarity factor in drug release in comparison the reference product, with good floating ability.

4. **SwarnkarKedar Prasad*et al.*[17]** reported on the Preparation and Optimization of oral floating alginate gel beads of famotidine. The objective was to prepare and optimize an oral floating alginate gel beads of famotidine using gas generating agent like sodium bicarbonate and Corn oil. The effect of different concentrations of sodium alginate, calcium chloride and famotidine were used and their Morphological analysis, Buoyancy, Encapsulation efficiency and *in-vitro* drug release behavior in simulated gastric fluid were carried out. Size of all the beads was found spherical and uniform and Buoyancy study showed that only F-3 to F-13 was floating. It was clearly seen that famotidine release from uncoated beads in a considerable "burst" during the first 30 min, due to rapid water ingress and creation of aqueous channels.

5. **Mohd Abdul Hadi*et al.*[18]**developed Floating multiple unit controlled-release beads of Zidovudine for the treatment of AIDS. The controlled release beads was prepared by Ionotropic gelation method using sodium alginate containing $KHCO_3$ as the gas-forming agent. The beads were subjected to in-vitro drug release, kinetic studies and stability studies. FTIR and DSC showed there was no interaction between drug and polymers.The percentage drug content in the beads ranged from 93.76±0.44 to 98.14±1.10 and the in-vitro percentage release from the beads at the end of 12 hours ranged from 86.10 to 96.83. The kinetics study revealed that the drug was released by zero-order kinetics. The stability studies

showed that there were no significant changes in drug content, physiochemical parameters and release pattern.

6. **Azhar Danish khan *et al*.**[19] formulated and evaluated Floating beads of verapamil hydrochloride. Emulsion gelation technique was used to prepare emulsion gelation beads using sodium alginate as the polymer. The effects of factors like concentration of oil, drug:poymer ratio and alginate:pectin ratio on entrapment efficiency , floating lag time, morphology and drug release were studied. The gel beads prepared with combination of alginate and pectin showed greater sustainability compared to alginate in terms of drug release. The results show that these beads can entrap even a water soluble drug as Verapamil hydrochloride in sufficient amount and also can successfully deliver the drug in stomach for a prolong duration of time without using any organic solvent and any time consuming step in the preparation.

7. **SundharamoorthyRevathi*et al*.**[20]formulated and evaluated Stavudine loaded Sodium alginate beads by Ionotropic gelation method. The objective of the present study was to develop hydrophilic and hydrophobic polymer based novel control release Stavudine beads for achieving the action upto 12 hours and to characterize the efficacy and to [analyze] the effect of various polymers like sodium alginate, HPMC and ethyl cellulose. From the results, it was stated that the formulation F-4 appears to be promising system for the sustained release for antiretroviral therapy based on actual drug content, % encapsulation efficiency and *in-vitro* drug release data.

8. **Elmeshad AN *et al*.**[21]reported on the Floating Furosemide gel beads: *in-vitro* and *in-vivo* evaluation. Buoyant beads enclosing furosemide were prepared by cross-linking chitosan with dioctyl sodium sulphosuccinate (DOSS) and characterized according to: entrapment efficiency, in vitro release, in vitro and in vivo buoyancy. The effect of various factors (DOSS and chitosan concentrations, drug: polymer ratio and loading technique) on bead properties were assessed.

Interaction between chitosan and DOSS was evaluated by DSC and FTIR. SEM demonstrated that the dried beads were spherical in shape with an inward cavity enclosing furosemide in the range of 1.8-62.25 %. Most beads floated over SGF for 12 h. Beads retarded the release of furosemide compared to pure drug powder and Lasix tablets. The t50 % ranged from 1.79-4.1 h and release followed zero or diffusion kinetics. Beads remained buoyant in the stomach of dogs for 6 h. Beadswere stable at 40°C and 75 % RH for 3 months.

9. **JharanaMallick *et al*.**[22]developed Alginate beads of Ibuprofen for oral sustained drug delivery: An in-vitro evaluation.Alginate beads were formulated under different conditionsof polymer concentration at constant speed. The beads were evaluated according toparticle size, drug content, percentage yield, moisture content by Karl Fischer titration, bulkdensity, tapped density, Carr's index. In vitro release of Ibuprofen from the beads wasstudied in simulated intestinal fluid (SIF, pH 7.4). The investigation revealedthat the beads produced with 2.5% (W/V) sodium alginate had the optimum prolongedrelease pattern. The beads produced using 2% (W/V) Sodium alginate had the highestdelayed release of the incorporated drug, whereas other ratios of drug polymer had the fastestrelease. The *in-vitro* dissolution studies appeared to have adequately described the releaseprocess as about 8 to 10 hours. The SEMstudy revealed thespherical shape and the presence of pores which is effective for loading of the dose. The X-Raydiffraction study, DSC, TGA and FTIR spectroscopy showed no drug polymer interaction.This impliesthat formulations of Ibuprofen-sodium alginate microspheres are likely to offer a reliable meansof delivering Ibuprofen by the oral route.

10. **Murata Y *et al*.**[23] studied on the Use of floating alginate beads for stomach-specific drug delivery.Two types of alginate gel beads capable of floating in the gastric cavity were prepared. The first, alginate gel bead containing vegetable oil (ALGO), is a hydrogel bead and its buoyancy is attributable to vegetable oil held in the alginate gel matrix. The model drug, metronidazole (MZ), contained in

ALGO released gradually into artificial gastric juice, the release rate being inversely related to the percentage of oil. The second, alginate gel bead containing chitosan (ALCS), is a dried gel bead with dispersed chitosan in the matrix. The drug-release profile was not affected by the kind of chitosan contained in ALCS. When ALCS containing MZ was administered orally to guinea pigs, it floated on the gastric juice and released the drug into the stomach. Furthermore, the concentration of MZ at the gastric mucosa after administration of ALCS was higher than that in the solution, though the MZ serum concentration was the same regardless of which type of gel was administered. These release properties of alginate gels are applicable not only for sustained release of drugs but also for targeting the gastric mucosa.

11. **Thakur AtulkumarRanvirsingh *et al.*[24]**formulated and evaluated Floating Alginate Beads of an Anti Ulcer Drug. The present research work was focused on the development of a multiple unit floating formulation using naturalpolymers (sodium alginate and Xanthan gum) and gas-forming agent(sodium bicarbonate) by employing ionotropic gelation method with Esomeprazole as a model drug. The formulated beads were characterized for particle size, percentage drug entrapment efficiency, *in-vitro* buoyancy and *in-vitro* drug release. Percentage drug entrapment was between 52.5% - 87.5 % and buoyancy was found to be between 84% - 98%. The *in-vitro* drugrelease results indicated that increasing the concentration of sodium alginate with respect to the drug resulted in further retardingthe drug release.

12. **Pranav Kumar Reddy M *et al.*[25]**prepared and evaluated Atenolol floating alginate beads as a controlled drug delivery system. Atenolol floating microspheres were prepared by the ionotropic gelation technique using HPMCand sodium alginate as polymers at different ratios. The 30ml of sodium alginate and HPMC solution in 9:1 ratio was prepared using 1%, 2% and 3% concentrations of polymers. The prepared formulations were characterized for their particle size, entrapment efficiency, drug content, and *in-vitro* drug release using 0.1N Hcl of

pH 1.2. The microspheres were found to be regular in shape and highly porous. Amongst 3 formulations prepared (F1-F3), F3 showed prolonged drug release and remain buoyant for more than 8 hours and suggested that increased polymer concentration gives slower release of drug and more duration of drug release in the stomach.

13. **Tapan Kumar Giri*et al.*[26]** reported on the Crosslinked biodegradable alginate hydrogel floating beads for stomach site specific controlled delivery of Metronidazole. In the present work, gastro retentive floating beads of sodium alginate (SA) were prepared through Ionotropic gelation with divalent Ca++ ions and covalent cross-linking with glutaraldehyde (GA). Metronidazole (MZ) was successfully encapsulated into beads by varying the amount of SA, xanthan gum, magnesium stearate, and GA. Encapsulation of MZ was up to 79.17%. However, with an increasing amount of GA in the matrix, the encapsulation efficiency was found to decrease significantly. Beads prepared without GA released 50% of the drug in 2.76h. GA treatment suppressed the drug release significantly. Compatibility of the drug with the polymers was examined using FTIR spectroscopy. DSC and X–ray diffraction studies XRD were carried out to examine the crystalline nature of the encapsulated drug. The drug was relatively stable and amorphous in the beads.

14. **Amal El Sayeh F *et al.*[27]**reported on Ketorolac tromethamine floating beads for oral application: Characterization and *in-vitro/in-vivo* evaluation.In the present work, the KT floating beads were prepared by extrusion congealing method utilizing calcium carbonate as a gas forming agent. The physical characters of the produced beads were investigated such as KT yield, KT loading, and entrapment efficiency of the drug. In addition, floating behavior, swelling, particle size, morphology and KT stability were also evaluated. *In-vitro* drug release study was carried out, and the kinetics of the release was evaluated using the linear regression method. Furthermore, the in vivo analgesic effect of KT after oral administration of the selected formula of floating beads (F10) was carried out

using hot plate and tail flick methods. Oral commercial KT tablets and KT solution were used for the comparison. The prepared beads remained floated for more than 8 h. The optimized formulation (F10) exhibited prolonged drug release (more than 8 h) and the drug release follows the Higuchi kinetic model, with a Fickian diffusion mechanism according to Korsmeyer- Peppas (n= 0.466). Moreover, F10 showed a sustained analgesic effect as compared to the commercial tablet.

15. **RammohanBera*et al.*[28]**formulated and evaluated (*in-vitro)* of Sunflower Oil Entrapped within Buoyant Beads of Furosemide.Sunflower oilentrapped buoyant alginate beads of furosemide were prepared by theemulsion-gelation technique. During the preparation of various batches ofbeads, the ratio of sunflower oil to water (v/v), the ratio of drug to polymer (w/w),were kept as variables at two levels; either high or low. Smooth, sphericalbeads with nominal weight variation were obtained. All batches of beads floatedfor 24 hours with a lag time of 5–10 min. The release of drug followed for5 hours. Higuchi and first order kinetic modeling indicated a diffusion-controlledrelease of drug from the beads. The study also demonstrated the influence ofsunflower oil on drug entrapment (81–95%) and *in-vitro* release. A higher levelof oil increased drug entrapment efficiency but retarded drug release rate ascompared to a lower level of oil containing beads.

16. **Karunapriyachitra*et al.*[29]**reported on A helping hand for prinzmetals-Nifedipine floating beads. The work was aimed at investigating the floating bead formulations prepared by ionotropic gelation technique. The formulations were optimized for different weight ratios of sodium alginate and gas forming agent(Calcium carbonate). FH1(HPMC1:1), FH2 (HPMC1:2), FP1(PVP1:1) , FP2(PVP1:2) were evaluated for percent drug loading, drug entrapment efficiency, surface topography, buoyancy, in vitro release and release kinetics. FT-IR results have shown that drug and excipients are compatible. FH2 shows better gastro retention (69.62%), buoyancy property throughout the study and

results drug entrapment efficiency (83.3%), percent drug loading (82.3%) and release patterns are better compared to other formulations. The beads containing higher amounts of calcium carbonate demonstrated instantaneous, complete and excellent floating ability over a period of 24 hrs. This above mentioned formulation (FH2) could be a suitable composition for Nifedipine as a floating gastro retentive dosage form.

17. **Yadav M *et al*.**[30]formulated and evaluated sustain release floating beads of anti hypertensive drug Ramipril. Drug and polymer compatibility was studied by subjecting physical mixtures of drug and polymers to FTIR. The beads were prepared by Ionotropic gelation method utilizing calcium carbonate as a gas forming agent. As gas-forming agents increased, the size and floating properties increased. The different concentrations of sodium alginate were used and their Morphological analysis, Buoyancy, Encapsulation efficiency and *in-vitro* drug release behaviour in simulated gastric fluid were carried out. The enhanced buoyancy and sustained release properties of CaCO3-containing beads make them an excellent candidate for floating drug dosage systems.

18. **Lohithasu D *et al*.**[31]reported on Formulation development and evaluation of glyburide beads for controlled release.Beads were successfully prepared by Ionotropic Gelation Method using Sodium alginate, HPMC K100M, Carbopol 940 and Calcium Chloride(fused) .The prepared beads were evaluated for various parameters like encapsulation efficacy, swelling index, Mean particle size, flow properties and in vitro release. The yields were varies from 88-93.8% and encapsulation efficacy is up to 91.2% which encourage the investigation. The dissolution was performed for 12 hours and the drug release was found to be 99.42%..The *in-vitro*release kinetics showed that it follows zero order. Hence, controlled release.

19. **SmritiMalviya*et al*.**[32]formulated and evaluated floating microbeads of Ciprofloxacin HCl by Emulsion gelation methodusing sodium alginate as the

polymer. The effects of factors likeconcentration of oil, curing time, drug: polymer ratio, alginate: pectin ratio and curing agent on drug entrapment efficiency, floating lag time, morphology and drug release were studied. Minimizing the curing time of beads leaded to enhanced drug entrapment efficiency. The use of sodium alginate and combinations of sodium alginate and pectin are used to study the effect on the sustaining property of the formed beads. It was found that sodium alginate was not sufficient to sustain the drug release at gastric pH. Instead of it, appropriate combination of alginate and pectin could provide the sustain release of drug. The results show that these beads can entrap even a water soluble drug as Ciprofloxacin in sufficient amount and also can successfully deliver the drug in stomach for a prolong duration of time.

20. **PeeushSinghal*et al*.**[33]reported on Evaluation of Acyclovir loaded oil entrapped calcium alginate beads prepared by Emulsion Gelation method by altering polymer: cross linking agent ratio (sodium alginate/ Calcium chloride), oil concentrations (10%, 20% and 30% w/w) and drug: polymer (D: P) ratios (1:1, 2:1 and 3:1). The beads were evaluated for diameter, surface morphology, encapsulation efficiency, buoyancy and invitro release. The results indicated that the percentage of oil plays an important role in controlling the floating of oil-entrapped Calcium alginate beads. *In vitro* drug release in the fed state conditions demonstrated sustained release of Acyclovir for 8 h, which best fitted the Higuchi model with $n < 0.5$. Calcium alginate beads containing 20% oil and 2:1 D: P ratio showed an optimum DEE (89.54%). Scanning electron microscopy revealed that the beads were spherical in shape with rough surface.

21. **BrahmaiahBonthagarala*et al*.**[34]formulated and evaluated extended release alginate beads of cefixime. Cefixime alginate beads were prepared by orifice-ionotropic gelation methodusing polymers such as HPMC (K 100 M), Carbopol 940P, Sodium CMC, Guar gum,Sodium Alginate, Ethyl Cellulose, Methyl Cellulose and Xanthan gum. Thealginate beads were characterized for drug content, entrapment efficiency, mucoadhesiveproperty by *in vitro* wash-off test

and *in-vitro* drug release. The ideal formulation was selected based on the *in-vitro* release profile which shows anextended drug release of 97.11% upto 8 hours in phosphate buffer of pH 7.0. The alginate beads were smooth andelegant in appearance showed no visible cracks as confirmed by SEM and FT-IR studiesindicated the lack of drug-polymer interactions in the ideal formulation (F10).The ideal formulation (F10)followed Higuchi kinetics and value of "n" is calculated to be 0.86 indicated that the drugrelease shows non-fickian diffusion.

22. **MitraJelvehgari*etal*.**[35]prepared Chlorpheniramine Maleate-loaded Alginate/Chitosan particulate systems by Ionic Gelation method for taste masking.The effect of different chitosan and ca2+ concentrations on taste masking and the characteristics of the microsphers were investigated. Formulations were characterized for particle size and shape, entrapment efficiency, FTIR, XRD, DSC, bitter taste threshold and *in-vitro* drug release study.The results of DSC, X-ray diffraction and FTIR showed the presence of several CM chemical interactions with alginate and ions (Ca2+ and Al3+). The microsphere formulations showed desirable drug entrapment The results of DSC, XRD and FTIR showed the presence of several CM chemical interactions with alginate and ions (Ca2+ and Al3+). The microsphere formulations showed desirable DEE's(62.2-94.2%). Calcium/aluminum alginate retarded the release of CM at low pH = 1.2 and released the drug from microspheres slowly at pH = 6.8, simulating intestine pH.

23. **Inderbirsingh*et al*.**[36]formulated and evaluated Domperidone loaded mineral oilentrapped emulsion gel buoyant bead by Emulsion gelation technique. The prepared beads were evaluated for particle size, surface morphology, buoyancy, actual drug content and entrapment efficiency. Effect of different oils (castor oil, olive oil and linseed oil) and oil concentrations (10%, 15% and 20%w/w) on uniformity, homogeneity and integrity of the beads was also studied. The results of the *in-vitro*drug release indicated that linseed oil showed to be good release retardant comparedto castor oil and olive oil. Moreover, the beads formulated

using 15% w/w linseed oil were more uniform in shape, exhibited maximum buoyancy and minimal oil leakage. Diffusion exponent (n) value varied from 0.4855 to 0.7710 indicating anomalous drug release behavior involving swelling, diffusion and/or erosion of the polymer matrix.

24.**PeeushSinghal*et al*.**[37]preparaed and evaluated stomach-specific ion tropically emulsion gelled alginate beads of Tinidazole. Tinidazole loaded Oil entrapped floating beads prepared by the emulsion gelation method were optimized for polymer: cross linking agent ratio (sodium alginate/ Calcium chloride),oil selection (olive oil and castor oil), oil concentrations (10%, 20% and 30% w/w) and drug:polymer (D: P) ratios (1:1, 2:1 and 3:1). The prepared beads were evaluated for diameter, surface morphology, encapsulation efficiency, buoyancy and in-vitro release. The calcium alginate beads remained buoyant for times in excess of 12 h, and the density of the calcium alginate beads was <1.000 g cm. The results clearly indicated that the percentage of oil plays an important role in controlling the floating of oil-entrapped Calcium alginate beads. In vitro drug release demonstrated sustained release of Tinidazole for 8 h, which best fitted the Higuchi model with n < 0.5. Calcium alginate beads containing 20% oil and 2:1 D: P ratio showed an optimum DEE (92.44 %). Scanning electron microscopy revealed that externally the calcium alginate beads were spherical in shape, and internally, air filled cavities were present thereby enabling floatation of the beads.

25. **Bhatt m b *et al*.**[38]formulated and evaluated ionotropically gelled novel hydrogel beads of valsartan using different ratio of polymer i.e. gellan gum and counter ion like calcium chloride in order to increase the drugbioavailability, therapeutic efficiency, reduce dosing frequency and improvement of patientcompliance. Drug- excipients compatibility was carried out by FTIR. Different formulations were evaluated for particle size, swelling index, % drug entrapment efficiency and *in-vitro* drug release. Optimized batch was evaluated for SEM.*In-vitro* release data was fitted to various models to ascertain the kinetic of drug release.A 32 factorial was applied to check the effect of varying the concentration of gellan gum

(X1) and calcium chloride (X2) on the dependent variable i.e. swelling index and *in-vitro* drug release. It was observed that optimized batch containing gellan gum(2.5%) and calcium chloride (4%) gives 123 % swelling index after 12 hrs and 100.56 % drugrelease after 24 hrs.

26. **Arunkumar B*et al*.**[39]formulated and evaluated gastro retentive floating microbeads of sumatriptan. The aim was to develop gastro retentive floating microbeads which improve the absolute bioavailability of Sumatriptan by avoiding the presystemic metabolism and thereby to reduce the dose frequency. Drug and polymer compatibility was studied by FTIR spectrophotometry, capability of floating in the gastric condition was evaluated. The beads were prepared by Ionotropic gelation methodusing Sodium alginate, HPMC K4M and Guar gum grade in 1:1, 1:2, 1:3 ratios. The beads were evaluated for percent drug entrapment efficiency, and *in-vitro* drug release. The *in-vitro* drug release study of the beads was carried out in simulated gastric media by USP dissolution method. Beads formulated employing Sodium alginate alone could not sustain the drug release, whereas beads formulated with mixture of Sodium alginate and copolymers demonstrated sustained release of Sumatriptan for 12h.

27. **BehinSundara Raj *et al*.**[40]formulated and evaluated chitosan Prazosin beads by Ionotropic gelation method. Prazosin loaded chitosan polyelectrolyte complex (PEC) hydrogel beads were prepared via ionotropic gelation and ionotropic crosslinking with sodium tripolyphosphate (TPP). A combination of Eudragit polymer was studied with chitosan having Prazosin dispersed within them. Thus, prazosin dispersed in 2% glacial acetic acid and having chitosan and polymer dispersed within. It was cross linked with 2% sodium tripolyphosphate solution adjusted to a pH of 4.5-6. The beads prepared were examined for the optimal stirring conditions and curing time in order to obtain spherical beads. Beads were prepared by three different drug: polymer ratios (1:1, 1:1.5, 1:2). Spherical to oval beads with varying particle size, weight, drug entrapment efficiency (DEE), and sustained release profile were obtained depending on the drug and polymer

combination used. The *in-vitro* dissolution rate profile showed a sustainedrelease of the drug from the beads over a 7 hour study period. Prazosin release decreased withan increasing concentration of chitosan.

28. **Mahmoud M Ahmed *et al.*[41]**reported on Emulsification/internal gelation as a method for preparation of diclofenac sodium–sodium alginate microparticles as controlled release microparticles that might be administered once or twice daily. This could be achieved by applying Box-Behnken design to choose these formulae. Box-Behnken design determined fifteen formulae containing specified amounts of the independent variables, which included stirring speed in rpm (X1), drug:polymer ratio (X2) and the surfactant span 80% (X3). The dependent variables studied were cumulative percent release after two hours (Y1), four hours (Y2) and eight hours (Y3). The prepared microparticles were characterized for their production yield, sizes, shapes and morphology, entrapment efficiency and Diclofenac sodium in vitro release as well. The formulated microparticles exhibited acceptable drug content values that lie in the range 66.20–96.36%. Also, the data obtained revealed that increasing the mixing speed (X1) generally resulted in decreased microparticle size. However, by increasing surfactant concentration, microspheres' surfaces become smoother and slightly porous. Kinetic treatment of the in vitro release from drug-loaded microparticles indicated that the zero order is the drug release mechanism for the most formulae.

29. **Baljit Singh *et al.*[42]**developed Gastro retentive floating sterculia–alginate beads for use inantiulcer drug delivery by Ionotropic gelation using CaCl2 as crosslinker. The beads thus formed were characterized by SEM, electron dispersion X-ray analysis (EDAX), FTIR spectroscopy. The swelling of beads has been carried out as a function of various reaction parameters and pH of the swelling media. In addition, *in-vitro* release dynamics of anti-ulcer model drug Pantoprazole from drug loaded beads in different release media has been carried out for the evaluation of the drug release mechanism and diffusion coefficients. Release of drug from beads occurred through Fickian type diffusion mechanism.

30. **Asha patel *et al*.**[43]reported on *in-vitro* evaluation and optimization of controlled release floating drug delivery system of Metformin hydrochloride.In the present study, preparation of Metformin hydrochloride floatingmicrospheres, evaluation of FDDS*in-vitro*, prediction of the release,and optimization of floatation and drug release pattern to match target release profile was investigated.Floating microspheres were prepared by non-aqueous emulsification solvent evaporation techniqueusing Ethylcellulose as the rate controlling polymer and 250 mg of Metformin hydrochloride per batchand its*in vitro* performance was evaluated by the usual pharmacopoeial and other tests such as drugpolymercompatibility (FTIR scan), yield (%), particle size analysis, drug entrapment efficiency, surfacetopography, and in vitro floatation and release studies. Results showed that the mixing ratio ofcomponents in the organic phase affected the size, size distribution (250-1000 μm), drug content(61 – 134% of theoretical load), yield (58– 87%) and drug release of microspheres (47 – 87% after 8 h),floating time (> 8 hr) and the best results were obtained at the ratio of drug: polymer: solvent(250:750:12 and 250:146.45:9 [mg: mg: ml]).

31. **Fursule RA *et al*.**[44] reported on Study of Multiparticulate Floating drug delivery system prepared by Emulsion gelation technique utilizing Amoxicillin trihydrate as the model drug. Different formulations of oil entrapped floating gel beads were prepared using sodium alginate as gelling agent. The prepared beads were evaluated for diameter, surface morphology and encapsulation efficiency. Greater percentage buoyancy and highest mean diameter was observed. Highest drug loading and SEM results showed that the beads are spherical in shape with rough surface and the in-vitro release study revealed that the beads showed sustained action for 12 h.

32. **Gattani Y S *et al*.**[45]formulated and evaluated gastro retentive multiparticulate drug delivery system of Aceclofenac by the emulsification solvent-evaporation technique consisting of Eudragit RS 100 as a polymer. The shape and surface morphology of prepared microsphere were characterized by optical and SEM. *In-*

vitro drug release studies were performed and drug release kinetics was evaluated using the linear regression method. Effects of polymer concentration, stirring rate during preparation and effect of temperature on size and drug release was evaluated. The prepared microspheres exhibited prolonged drug release (> 12h) and remained buoyant for > 12 h. *In-vitro* studies demonstrated diffusion controlled drug release from the microspheres.

33. **Pande AV *et al.*[46]**reported on floating microspheres of Cefpodoxime proxetil: formulation and optimization by factorial design. The microspheres were prepared by solvent evaporation (o/w emulsion) method using Eudragit S100. A 32 full factorial design has been applied. The variables conc. of ES100 and stirring speed was studied at three levels and arranged in 32 factorial design to study their influence on percentage drug release, percentage entrapment efficiency, and particle size. The physical characteristics of floating microspheres were evaluated using FTIR, DSC and SEM.

34. **Swathi S *et al.*[47]**reported on formulation and *in vitro* evaluation of floating microspheres of Atomoxetine Hcl. The floating microspheres were prepared by using bio compatible polymers like ethyl cellulose along with the drug in different proportions by Non-aqueous solvent evaporation method. The microspheres were characterized for micromeritic properties, percentage entrapment efficiency, percentage yield, Mean particle size, *in-vitro* buoyancy, *in-vitro* drug release studies. It was observed the increase in concentration of ethyl cellulose increases the entrapment efficiency and particle size of the microspheres. In-vitro drug release studies showed that release from microsphere get successfully retarded for 12 h.

35. **Rakesh Pahwa*et al.*[48]** formulated and evaluated of Floating Multiparticulate Drug Delivery System of Glipizide. Floating microspheres were prepared by Ionotropic gelation method using polymeric material such as chitosan. D-optimal design was utilized to investigate the joint influence of two variables: drug to

polymer ratio (X_1) and concentration of effervescent agent (X_2) on the drug entrapment efficiency, percentage buoyancy and cumulative percentage drug release. Particle size and surface morphology of prepared microspheres were characterized by optical and scanning electron microscopy respectively. Formulated microspheres exhibited prolonged drug release and remained buoyant for more than12 h.

36. **Keyur S Patel *et al.*[49]**prepared and evaluated chitosan microspheres containing nicorandil to reduce the dosing frequency. The nicorandil-loaded chitosan microspheres were formulated by emulsion crosslinking method. A 32 factorial design was employed to study the influence of drug: Polymer ratio and volume of glutaraldehyde on percentage entrapment efficiency, particle size, and % drug release at 8 h. The entrapment efficiency was found to be 41.67 ± 1.43-77.33 ± 1.97% and particle size range 65.67 ± 2.08-146.67± 2.18 µm. The batch CH5 showed 79.11 ± 2.23 and 96.21 ± 2.41% drug release at 8 and 12 h, respectively. Drug: Polymer ratio and volume of GA had significant effect on % entrapment efficiency, particle size, and % drug release. From the SEM study observed that microspheres were spherical and fairly smooth surface. Fickian diffusion was the mode of drug release from Nicorandil-loaded chitosan microspheres.

37. **Keyur S Patel*et al.*[50]**formulated and evaluated Eudragit Microspheres Containing Nicorandil using Eudragit RS 100 and Eudragit RL 100. The Nicorandil loaded Eudragit microspheres were formulated by non aqueous solvent evaporation method and study the effect of different grade of Eudragit and drug: polymer ratio on % Yield, % Entrapment efficiency, particle size and % drug release of microspheres. The Entrapment efficiency was found to be 82.31 ± 1.58% to 91.25 ± 2.54% and particle size range 60.25 ± 1.42µm to 92.21 ± 2.32µm. The Batch EU6 showed almost 100 % drug release at 12 hrs. % *In vitro* drug release was decreased with increasing the drug: polymer ratio. Drug release was high in Eudragit RL 100 microspheres compare to Eudragit RS 100 microspheres. Fickian diffusion was the mode of drug release from Nicorandil loaded Eudragit microspheres.

38. **Ju-Young Kim *et al.*[51]**designed and evaluated Nicorandil Extended-release tablet. The in vitro/in vivo relationship of the extended-release formulation was confirmed using in vitro dissolution profiles and plasma concentrations of drug in beagle dogs. Nicorandil was released completely within 30 min from the immediate-release tablets and released for 24 h from the extended-release tablets. The Nicorandil plasma concentration could be modified by adjusting the drug release rate from the extended-release formulation. The release rate of nicorandil was the rate-limiting step in the overall absorption of drug from the extended release formulations. These results highlight the potential of a nicorandil extended-release formulation in the treatment of angina pectoris.

39. **Abdul** B**aquee Ahmed *et al.*[52]**reported on drug- excipients compatibility studies of Nicorandil in controlled release floating tablet.DSC, Isothermal stress testing (IST) and with the support of Fourier transform infrared spectroscopy (FT-IR) were used to evaluate compatibility of drug-excipients mixture. The optimized formulation developed using the compatible excipients were evaluated for 3 months of stability studies at 2-8°C and 25°C/60% RH.The results of DSC, IST and FT-IR studies confirmed the absence of incompatibility of Nicorandil with the excipients used in the formulations. The result of stability studies shows that the formulations ware more stable at refrigerator (2-8°C) than stored at 25°C/60%RH. Besides, the selection of proper excipients storage condition will also plays an important role in development of stable dosage form for Nicorandil.

40. **Swati Chaturvedi*et al.*[54]**reported on Comparison of Emulsification and Ionic Gelation **Method** of Preparation of Mucoadhesive Microsphere. The purpose of this study was to prepare and characterize microspheres loaded by Aceclofenac. To achieve this goal Chitosan and Sodium alginate microspheres loaded by Aceclofenac were prepared by emulsification and ionic gelation methods. Morphology, size, encapsulation efficiency and drug release from these microspheres were evaluated. Microscopic evaluation of microspheres showed that microspheres were spherical in shape. The size analysis results indicated that

size range varied from 1 to 13 μm. Encapsulation efficiency of microspheres was increased by increasing drug to polymer ratio. Drug release was found to be Zero order.

AIM OF THE WORK

- ✓ The main objective of the present study is to develop Capsules containing Nicorandil loaded oil entrapped floating alginate beads for the treatment of Angina pectoris.
- ✓ The floating beads have been employed to make a sustained release of the drug in the stomach to enhance bioavailability and to decrease dose dumping and hence overcome its side effects.
- ✓ To optimize the Nicorandil loaded oil-entrapped floating alginate beads by Emulsion Gelation method with various Sodium Alginate concentration (2%w/v, 3%w/v, 4%w/v), Drug:Polymer ratio(1:0.5,1:1,1:2) and various oil concentration 15%v/v,20%v/v.
- ✓ To capsulate and evaluate the optimized batch of Nicorandil loaded oil entrapped floating alginate beads.

PLAN OF WORK

- Preformulation studies.
  - Compatibility studies
- Construction of Calibration curve.
- Formulation of Nicorandil loaded oil entrapped floating alginate beads.
- Evaluation of Nicorandil loaded oil entrapped floating alginate beads.
  - Percentage yield
  - Study of size and Morphology of Alginate beads.
  - Percentage Entrapment Efficiency and Drug Loading.
  - Density of beads.
  - Swelling studies.
  - *In-vitro* floating properties.
  - *In-vitro* drug release studies.
- Preformulation studies for Capsules.
  - Bulk density.
  - Tapped density.

  - Angle of repose.
  - Carr's index.
  - Hausner's ratio.
- Capsulation of the optimized Nicorandil loaded oil entrapped floating alginate beads.
- Evaluation of Capsules.
  - Uniformity of weight.
  - Disintegration time.
  - *In-vitro* drug release studies.
- Similarity factor
- Evaluation of release kinetics.
- Stability studies.

RATIONALE FOR SELECTION OF NICORANDIL [52,55,63]

- ✓ Nicorandil is used therapeutically in the long term treatment of Angina pectoris.
- ✓ Nicorandil is primarily absorbed from the upper GI tract and has a elimination half life of 1 hour and it is administered orally as 5-20 mg twice daily (usual dose) in order to maintain the constant plasma level.
- ✓ The drug has better solubility in acidic medium. An increase in gastric retention time may increase the extent of absorption of the drug. It is more suitable to formulate as floating systems for achieving regular and constant plasma levels.
- ✓ Nicorandil is believed to exert myocardial protection by a process of ischaemic preconditioning which appears to reduce myocardial stunning, arrhythmias and infarct size when a coronary artery is suddenly blocked in addition to vasodilatation which is lacked by other vasodilators. Hence, Nicorandil is preferred over other vasodilators.

RATIONALE FOR SELECTION OF DOSAGE FORM[1,4,9,14,15,16]

- ✓ Gastro retentive dosage forms have been developed to improve the clinical efficacy of the drug having short half life as well as to improve the patient compliance.
- ✓ Single unit formulations are associated with problems such as sticking together or being obstructed in gastrointestinal tract, which may have a potential danger of producing irritation.
- ✓ Multiple unit systems **avoid the 'all-or-none' gastric emptying nature of single unit systems.** It reduces the intersubject variability in absorption and the probability for dose dumping is lower.
- ✓ Preparation of floating alginate beads is more suitable because it is a multiparticulate system, utilizes cheap and non-toxic polymers and there is no use any organic solvent.
- ✓ The floating beads have been employed to make a sustained release of the drug in the stomach and to decrease the dose of the drug and hence overcome its side effects.

- ✓ Oil entrapped Floating alginate beads is prepared by Emulsion gelation method. The entrapped oil aids in the floating of the beads for a prolonged period of time within the gastric region.
- ✓ Sodium alginate, a hydrophtilic polymer has been selected since it retards the release of the drug from the dosage form (sustained action) and it is biodegradable in nature.

Angina, also called Angina pectorismeaning ***ankhon = strangling;pectis = chest*** - is a symptom of an underlying heart condition. It means that the heart is not getting enough blood and as a result, not enough oxygen. This decrease of oxygen being delivered to the muscle of the heart happens if one or more coronary arteries are narrowed or blocked, a condition called **atherosclerosis**.[56,57]

This type of blockage may result in chest pain. And while angina does not usually damage the heart, and the pain might only last a few minutes, it isa warning sign and it should not be ignored.[56]

An angina attack is **not** the same as a heart attack, although many of the symptoms are the same. An angina attack may be provoked by extremes in emotion (being very angry or upset), eating a large meal or eating it very quickly, doing more exercise than usual (overexerting yourself), being exposed to extremes in temperature (too hot or too cold), or smoking. If the angina is a result of physical activity, stopping the activity generally stops the pain. But no matter what the cause of the chest pain or discomfort, it is important to get medical attention as soon as possible.[56]

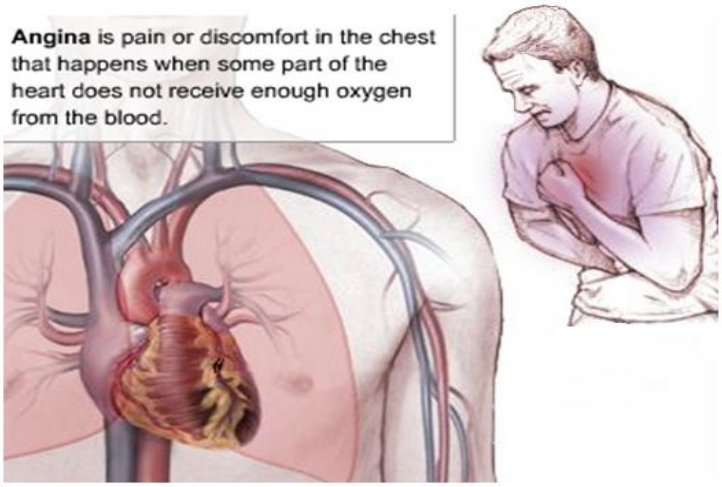


Fig.12: Angina pectoris

BACKGROUND[58]

Angina pectoris is the result of myocardial ischemia caused by an imbalance between myocardial blood supply and oxygen demand. Angina is a common presenting

symptom typically chest pain among patients with coronary artery disease. A comprehensive approach to diagnosis and to medical management of angina pectoris is an integral part of the daily responsibilities of health care professionals.

EPIDEMIOLOGY[59,58]

As of 2010, angina due to ischemic heart disease affects approximately 112 million people(1.6% of the population) being slightly more common in men than women.(1.7% to 1.5%).

Angina is more often the presenting symptom of coronary artery disease in women than in men. The prevalence of angina rises with increasing age, with a mean age of onset of 62.3 years. After five years post-onset, 4.8% of individuals with angina subsequently died from Coronary heart disease(CHD).

Men with angina were found to have an increased risk of subsequent acute myocardial infarction and coronary heart disease related death than women. Similar figures apply in the remainder of the western world. As its risk factors are more common in western and westernized countries, it could be termed as *disease of affluence*The adoption of a rich, westernized diet and subsequent increase of smoking, obesity and other risk factors had led to an increase in angina and related diseases in countries such as China, India.

ETIOLOGY AND PATHOPHYSIOLOGY[60,61]

Angina pectoris occurs when cardiac workload and resultant myocardial oxygen demand exceed the ability of coronary arteries to supply an adequate amount of oxygenated blood. This can occur when the arteries are narrowed. Narrowing of arteries results from atherosclerosis but may results from coronary artery spasm or rarely, coronary artery embolism. Due to myocardium ischemia, the myocardial tissues are deprived of oxygen and nutrients for the aerobic metabolism. As aresult there is an inclusion of anaerobic metabolism which leads to accumulation of lactic acid.

Due to increase of lactic acid, myocardial nerve fibres are irritated and this transmit a pain message to the cardiac nerves and upper thoracic posterior nerve roots. All this leads to cardiac pain, the Angina.

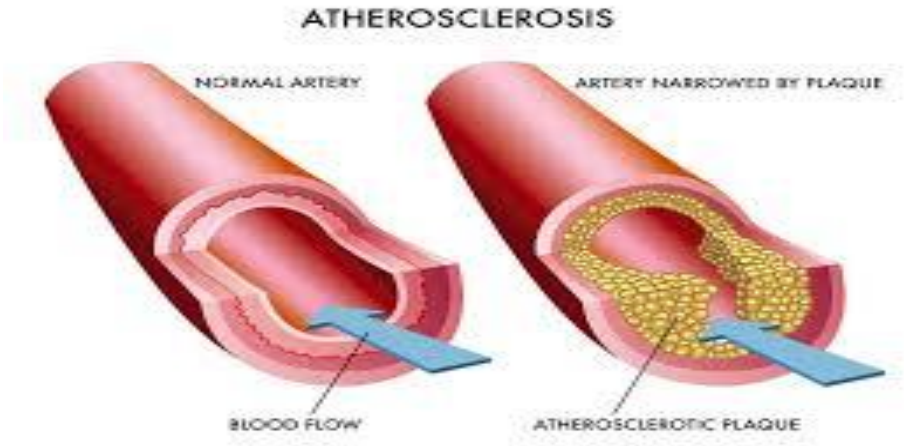


Fig.13: Atherosclerosis

TYPES OF ANGINA[56,59,62]

Five different kinds of angina have been identified, with the two most common being **Stable angina** and **Unstable angina**.

1. Stable (typical) angina

- The most common form of angina
- Consequence of coronary atherosclerosis
- Presents in physical activity(exercise), emotional stress etc.
- Predictable, reproducible (exertion) – The pain goes away in few minutes once the gets out of the stress or takes medications.
- Worse in cold conditions and after meals.

2. Unstable angina (crescendo/pre-infarction angina)

- Intermediate state between stable angina and MI.
- A presentation of "acute coronary syndromes" (ACS).
- May appear unexpectedly, at rest.

- Often not associated with physical activity.
- Usually a consequence of severe coronaryatherosclerosis possibly complicated by arupture and thrombus formation.
- People with unstable angina are at increased risk for heart attacks, cardiac arrest, or severe cardiac arrhythmias (irregular heartbeat or abnormal heart rhythm).
- Management issimilar to that of MI

3. Prinzmetal angina (variant/vasospastic angina)

- An uncommon form of angina.
- Consequence of coronary artery spasm – May cause severe pain.
- Occurs at rest (Usually between midnight and 8 am in the morning).
- Most people who have variant angina have severe atherosclerosis (hardening of the arteries), and the spasm is most likely to occur near a buildup of fatty plaque in an artery.

4. Microvascular angina

- Referred to as Syndrome X
- Occurs when tiny vessels in the heart become narrow and stop functioning properly, even if the bigger arteries are not blocked by plaque.
- Treated with common angina medications.

5. Atypical angina

- Often doesn't cause pain, but a vague discomfort in chest can be felt
- Experience shortness of breath, feel tired or nauseous, have indigestion, or pain in back or neck.
- Women are more likely than men to have feelings of vague chest discomfort.

RISK FACTORS[56]

- High blood pressure (for more on high blood pressure, click here)
- Diabetes
- Unhealthy cholesterol levels
- Smoking
- Lack of exercise
- Obesity
- Too much salt in diet
- Excessive use of alcohol
- Family history of CAD or stroke
- Male gender
- Being a postmenopausal woman
- Age - the risk increases for men over the age of 45 and for women over the age of 55.

SYMPTOMS[56]

The symptoms of angina are different for different people, but regardless, they are usually experienced after heavy exercise or because of emotional stress.

- Pain that begins in the middle of your chest and then spreads to your left arm, back, neck or jaw; usually this is not a sharp pain, but a dull one
- A feeling of pressure, tightness or squeezing in your chest or arms
- A feeling of persistent indigestion that is moderate or severe
- Numbness, or a lack of feeling in your arms, shoulders or wrists

The symptoms vary according to the type of angina.For example,if a person has **stable angina**, the pain or discomfort:

- Happens when the heart has to work harder, during exercise.
- Is no surprise and feels the same each time it happens.
- Usually lasts less than 5 minutes, and stops after taking rest or medication.
- It might feel like indigestion.

Unstable angina is different. The pain or discomfort:

- Often happens when while sleeping or resting.
- Might last as long as 30 minutes and might become progressively worse.
- Cannot be relieved with rest or medication.
- Might be a sign of a heart attack that will happen soon
- Unstable angina tends to happen more often in older adults.

Fig.14: Representing pain radiation

DIAGNOSIS[58]

Diagnostic studies that may be employed include the following:

A) Chest radiography

Usually normal in angina pectoris but may show cardiomegaly in patients with previous MI, Ischemic cardiomyopathy, pericardial effusion or acute pulmonary edema.

B) Gradedexercise stress testing

This is the most widely used test for the evaluation of patients presenting with chest pain and can be performed alone and in conjugation with echocardiography or myocardial perfusion scintigraphy.

C) Coronary artery calcium (CAC) scoring by fast CT

The primary fast CT methods for this application are electron-beam CT (EBCT) and multidetector CT (MDCT).

Other tests that may be useful include the following:

D) Electrocardiogram(ECG)

It involves hooking up to a machine that detects and records your heart's electrical activity. This is a painless procedure and does not take very long

E) Selective coronary angiography

The definite diagnostic test for evaluating the anatomic extent and severity of CAD.

F) Computed tomography (CT) scan

It is like a high-speed x-ray and show the amount of calcium present in the arteries. The level of calcium help to show whether coronary artery disease prevails.

If one or more of these tests do show positivity for angina, the diagnosis might be confirmed by undergoing **cardiac catheterization**. A special dye will be injected into the arteries and then photographs taken of them that allows the physician to see whether they are narrow.

TREATMENT[58]

The main goals of treatment in Angina pectoris are relief of symptoms, slowing progression of the disease and reduction of future events, especially heart attacks and death.

Lifestyle modifications

- Increased, controlled physical activity (exercise training)
- Smoking cessation
- Weight management, balanced diet

Pharmacotherapy[58,63]

Three major drug classes:

- Organic nitrates
- CCBs
- β-blockers

- **Nitrates** are available in a number of different forms.**Nitroglycerin** that can be taken under the tongue (called sublingual) or sprayed into the mouth works very quickly to relieve the pain of an angina attack, while other forms of nitroglycerin,

like tablets or patches, can be taken to help prevent an attack from starting. Headache is a possible side effect.

- **Beta-blockers** are a class of medicines used to treat several kinds of heart disease. They work by lowering blood pressure, and slowing heart rate which means the heart doesn't have to work as hard.
- **Calcium channel blockers** or **calcium antagonists** also work by lowering blood pressure and slowing heart rate, and are often used if you cannot take a beta-blocker. They may be useful to treat coronary artery spasm.
- **Antiplatelet** medications are blood thinners that work by preventing blood clots from forming and blocking your arteries. The most commonly used antiplatelet medication is **aspirin**, which works by preventing platelets from sticking to blood vessel walls. An enteric-coated aspirin is generally recommended because it is easier on the stomach. Other medications can be used to stop platelets from sticking together. They may be used to reduce the risk of clot-induced heart attacks or strokes.
    - Other medications that might be helpful in angina includes
- **Cholesterol-lowering drugs** known as statins can help to reduce the chance of a heart attack in someone with angina.
- **ACE inhibitors** which are used primarily to treat high blood pressure, may reduce the chance of heart attack in some people with angina, even if their blood pressure is normal.

Surgical procedures

Treating unstable angina sometimes requires surgical intervention, with or or without the previous use of medications. Two procedures are available:

Angioplasty is a procedure in which a small catheter (a little tube) is inserted into a narrowed or blocked artery. At the top of this catheter is a little balloon that the physician inflates when the catheter has reached the blocked part of the artery. The balloon, when inflated, helps to push the plaque against the wall of the artery. Once the balloon is deflated, it often opens up the blockage enough for more blood to flow through

the artery, and this should lessen the pain. In some cases, a small device called a stent will be put in place to help prop your artery open.

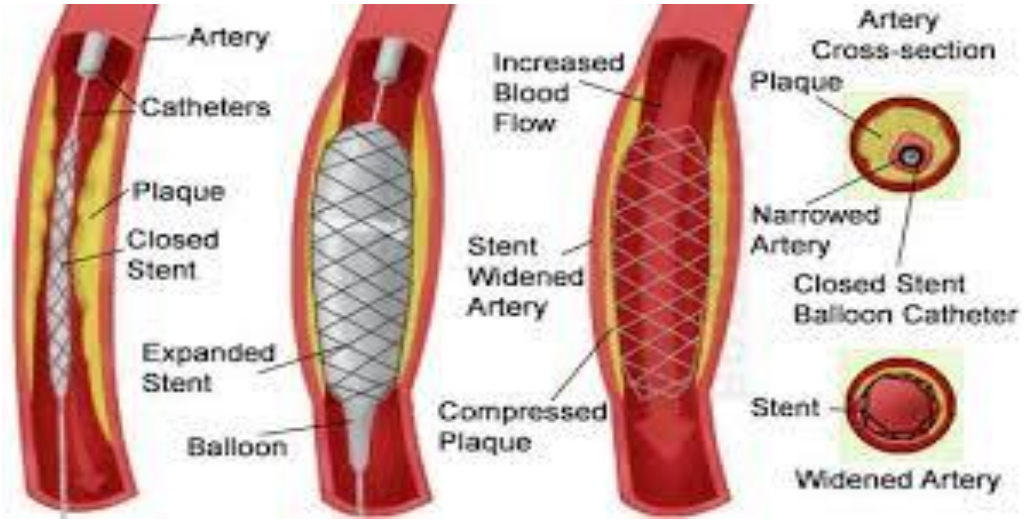


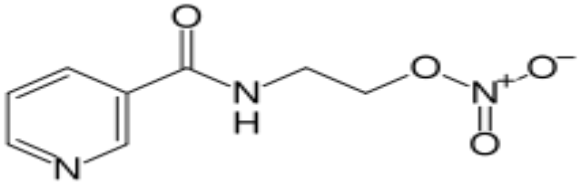
Fig.15: Angioplasty

If several arteries are severely blocked, **coronary artery bypass surgery** (also sometimes referred to as coronary artery bypass grafting or CABG) may be recommended. This procedure involves taking a healthy artery or vein from another place in your body (your leg, for example), and grafting it in your heart to help the blood go around (or bypass) the blockage.

NICORANDIL[63,64,65,66,67,68]

PHYSIOCHEMICAL PROPERTIES

Chemical structure:



Chemical Name : N-[2-hydroxyethyl] nicotinamide nitrate [ester]

Molecular Formula: $C_8H_9N_3O_4$

Molecular Weight : 211.175g/mol

Description : A white to off- white crystalline powder.

Melting point : 92ºC -93ºC

Solubility : Freely soluble in methanol, in acetone and in glacial acetic acid. Soluble in dichloromethane. Sparingly soluble in chloroform.

Density: 1.3g/cm^3

CAS Number : 65141-46-0

MECHANISM OF ACTION

Nicorandil activates ATP sensitive K+ channels- hyperpolarize the vascular smooth muscle.

Like Nitrates, it also acts as a NO donor – relaxes blood vessels by increasing cGMP. Thus, arterial dilatation is coupled with venodilatation. Coronary flow is increased and dilates bothepicardial conducting vessels and deeper resistance vessels. No significant cardiac effects on contractility and conduction are noted.

Mitochondrial k^+ ATP channel opening by Nicorandil is believed to exert myocardial protection by a process of ischaemic preconditioning which appears to reduce myocardial stunning, arrhythmias and infarct size when a coronary artery is suddenly blocked.

PHARMACOKINETICS

Absorption

Nicorandil is well absorbed from the gastrointestinal tract and maximum plasma concentration of nicorandil is linearly related to the administered dose. The urinary recovery data following oral administration of the drug indicated that more than 90% of the oral dose (20 mg) was absorbed. There is some evidence that consumption of food concurrently with the administration of Nicorandil can prolong drug absorption resulting in a delayed and decreased maximum plasma concentration.

Bioavailability

The absolute bioavailability of Nicorandil is75±23%, indicating that no significant first pass effect exists.

Half- life

1 hour

Distribution

After oral (and i.v.) administration of the drug, the apparent volume of distribution is approximately 1.0 L/kg body weight. The drug distribution in the body was reported that it follows two compartment model. It is very weakly bound to albumin (19.4%) and protein binding is found to be (23.3 %).

Metabolism

Nicorandil is metabolized extensively and the nicotinamide/nicotinic acid biotransformation pathway contributes to the accumulation of Nicorandil and 2-nicotinamidoethanol (denitrated metabolite)during repeated dosing because of the saturable merging of nicotinamide/nicotinic acid derivatives (from the Nicorandil metabolism) into the NAD/NADP endogenous pool of coenzymes. After metabolism the Nicorandil is converted primarily to the denitrated compound, SG-86 (N-2-hydroxyethyl nicotinamide), which is pharmacologically inactive.

Excretion

The major route of elimination is through kidney: Less than 2% of the dose is excreted through the biliary route. The total body clearance of Nicorandil is equal to 52 ± 18lit/hr, indicating that it is less than the liver blood flow.

THERAPEUTIC INDICATION

- Angina pectoris
- Hypertension

ROUTE AND DOSAGE

Adult : Oral :

- ✓ Initial dose - 10mg twice daily.
- ✓ Usual dose – 10-20mg twice daily.
- ✓ Maximum dose – 30mg twice daily.

CONTRAINDICATIONS

Contraindicated in patients with cardiogenic shock (poor blood circulation), heart failure, low blood pressure breast-feeding and children.

SIDE EFFECTS

- Most common – Headache, dizziness, drowsiness, nausea, vomiting, flushing, weakness and rectal bleeding.
- Heart – Fast heart rate and low blood pressure.
- Miscellaneous – Rash, abnormal liver function, mouth ulcer and muscle pain.

MARKETED FORMULATIONS

- K- COR
- KORANDIL
- NIKORAN
- NICODUCE
- ZYNICOR

SODIUM ALGINATE[69]

1. **Nonproprietary Names:**

   BP: Sodium alginate, PhEur: Natrii alginas, USPNF: Sodium alginate

2. **Synonyms:**

   Algin, alginic acid, sodium salt, E401, Kelcosol, Keltone, Protanal, sodium, Polymannuronate.

3. **Chemical Name:**

   Sodium alginate

4. **Empirical Formula and Molecular Weight:**

   Sodium alginate consists chiefly of the sodium salt of alginic acid, which is a mixture of polyuronic acids composed of residues of D-mannuronic acid and L-guluronic acid.

5. **Functional Category:**

   Stabilizing agent, suspending agent, tablet and capsule disintegrant, tablet binder, viscosity-increasing agent

6. **Description:**

   Sodium alginate occurs as an odorless and tasteless, white to pale yellowish brown colored powder.

7. **Solubility:**

   Practically insoluble in ethanol (95%), ether, chloroform, ethanol/water mixtures in which the ethanol content is greater than 30%. Also, practically insoluble in other organic solvents and aqueous acidic solutions in which the pH is less than 3. Slowly soluble in water forming a viscous colloidal solution.

8. **Applications :**

   Sodium alginate is used in a variety of oral and topical pharmaceutical formulations. In tablet formulations, sodium alginate may be used as both a binder(1-3%) and disintegrant(2.5-10%). It has been used as a diluent in capsule formulations. Sodium alginate has also been used in the preparation of sustained release oral formulations since it can delay the dissolution of a drug from tablets, capsules and aqueous suspensions.

In topical formulations, sodium alginate is widely used as a thickening and suspending agent (1-5%) in a variety of pastes, creams and gels, and as a stabilizing agent (1-3%) for oil-in-water emulsions. It has been used for the aqueous microencapsulation of drugs, in contrast with the more conventional microencapsulation techniques which use organic-solvent systems. It has also been used in the formation of nanoparticles. Sponges composed of sodium alginate and chitosan produce a sustained drug release

Other novel delivery systems containing sodium alginate include ophthalmic solutions that form a gel in situ when administered to the eye; an in situ forming gel containing Paracetamol for oral administration; and a freeze-dried device intended for the delivery of bone growth factors. Hydrogel systems containing alginate have also been investigated for delivery of proteins and peptides.

Alginate dressings, used to treat exuding wounds, often contain significant amounts of sodium alginate as this improves the gelling properties.

HYDROXY PROPYL METHYL CELLULOSE[69]

1. **Non-proprietary Name:**

   BP: Hypromellose, JP: Hypromellose PhEur: Hypromellose

   USP: Hypromellose

2. **Synonyms:**

   Benecel MHPC, E464, hydroxyl propyl methyl cellulose, HPMC Hypromellosum, methocel, methyl cellulose propylene glycol ether, methyl hydroxyl propyl cellulose, metolose, MHPC, Pharmacoat, Tylophor, Tylose

3. **Chemical Name:**

   Cellulose hydroxyl propyl methyl ether

4. **Molecular weight:**

   Molecular weight approximately 10000-1500000

5. **Functional category**:

   Bio adhesive material, coating agent, controlled release agent, emulsifying agent, film forming agent, suspending agent, sustained release agent, tablet binder.

6. **Description:**

   Hypromellose is an odourless and tasteless, white or creamy – white fibrous or granular powder.

7. **Solubility :**

   Soluble in cold water, forming a viscous colloidal solution; practically insoluble in hot water, chloroform, ethanol (95%) and ether.

8. **Applications:**

   HPMC is widely used in oral, ophthalmic, nasal and topical pharmaceutical formulations. It is used as tablet binder in film-coating and as a matrix for extended release tablet formulations, concentrations between 2-5% used as binder in either wet or dry granulation processes. High viscosity grades may be used to retard the release of drugs from a matrix at levels of 10-80%w/w in tablets and capsules. Hypromellose is also used in liquid oral dosage forms as a suspending and/or thickening agent at concentrations ranging from 0.25-5.0%.

CALCIUM CHLORIDE[64,70,71]

1. IUPAC Name:

Calcium chloride

2. Other Names:

Calcium(II) chloride, Calcium dichloride, E509

3. Molecular formula:

$Cacl_2$

4. Molecular weight:

110.984g/mol

5. Description:

White powder, Hygroscopic and odorless.

6. Density:

2.15 g/cm^3

7. Melting point:

772-775 ºC (anhydrous)

8. Boiling point:

1,935 ºC (anhydrous)

9. Solubility :

Highly soluble in water (74.5g/100ml - 20 ºC)

10. Applications:

- ✓ Desiccant
- ✓ Used as a cross-linking agent in the preparation of pharmaceutical formulations
- ✓ Used to quickly treat calcium channel blocker toxicity
- ✓ It is injected to treat internal hydrofluoric acid burns.

MINERAL OIL, LIGHT[69]

1. Nonproprietary Names

BP: Liquid paraffin ; JP: Liquid paraffin; PhEur: Paraffinum liquidum

USP: Mineral oil

2. Synonyms

905 (mineral hydrocarbons); Citation; light liquid petrolatum; light white mineral oil.

3. Chemical Name

Mineral oil

4. Empirical Formula and Molecular Weight

Light mineral oil is a mixture of refined liquid saturated hydrocarbons obtained from petroleum. It is less viscous and has a lower specific gravity than mineral oil.

5. Functional Category

Emollient, tablet and capsule lubricant, oleaginous vehicle, solvent therapeutic agent.

6. Description

Light mineral oil is a transparent, colorless liquid, without fluorescence in daylight. It is practically tasteless and odorless when cold, and has a faint odor when heated. The USPNF 23 specifies that light mineral oil may contain a suitable stabilizer.

7. Solubility

Practically insoluble in ethanol (95%), glycerin, and water; soluble in acetone, benzene, chloroform, carbon disulfide, ether, and petroleum ether. miscible with volatile oils and fixed oils, with the exception of castor oil.

8. Applications

Light mineral oil is used in applications similar to those of mineral oil. It is used primarily as an excipient in topical pharmaceutical formulations where its emollient properties are exploited in ointment bases(0.2-23%). It is also used in ophthalmic formulations(< 15%). Light mineral oil is additionally used in oil-in-water and polyethlylene glycol/gylcerol emulsions, as a solvent and lubricant in

capsules and tablets, as a solvent and penetration enhancer in transdermal preparations and as the oily medium used in the microencapsulation of many drugs. Light mineral oil is also used in cosmetics and certain food products.

MAGNESIUM STEARATE[69]

1. **Non-proprietary names:**

   BP:Magnesium stearate, JP: magnesium stearate, PhEur:magnesium stearate, USP- NF: Magnesium stearate.

2. **Synonyms:**

   Dibasic magnesium stearate, Magnesiudistearate, Magnesia stearas, Magnesium octadecanoate, octadecanoic acid, magnesium salt, Synpro 90.

3. **Chemical name:**

   Octa decanoic acid, Magnesium salt.

4. **Empirical formula:**

   C36H70MgO4

5. **Molecular weight:**

   591.24

6. **Functional category:**

   Tablet and capsule lubricant.

7. **Description:**

   Magnesium stearate is a very fine, light white, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

8. **Incompatibilities:**

   Incompatible with strong acids, alkalis and iron salts.

9. **Applications:**

   It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0%w/w. It is hydrophobic and may retard the dissolution of a drug from solid dosage form. The lowest possible concentration is therefore used in such formulations.

MATERIALS USED IN FORMULATION

Table 3: List of materials and their applications in the formulation

S.No.	Name of the material	Manufacturer/Supplier	Applications
1.	Nicorandil	Madras Pharmaceuticals Ltd.	Active ingredient
2.	Sodium alginate	Macleods Pharmaceuticals Ltd.	Hydrophilic Polymer
3.	HPMC K 100M	Kniss Laboratories	Hydrophilic polymer
4.	Liquid paraffin	Lab Chemicals	Oil phase
5.	Calcium chloride	Lab Chemicals	Cross-linking agent
6.	Magnesium stearate	Kniss Laborataries	Lubricant

EQUIPMENTS/INSTRUMENTS USED IN FORMULATION

Table 4: List of equipments/instruments used

S.No.	Equipment's / Instruments	Manufacturer / Supplier
1.	Electronic weighing balance	Asha scientific company, Mumbai
2.	Magnetic stirrer	REMI 1MLH
3.	pH meter	MC Dalal, Chennai
4.	Disintegration apparatus	Electrolab, India
5.	Dissolution tester	Campbell Electronics, India
6.	UV-visible spectrophotometer	Shimadzu, Japan
7.	Fourier Transform Infra-Red Spectrophotometer	Nicolet, India
8.	Scanning Electron Microscopy	Hitachi, Japan

METHODOLOGY

PREFORMULATION STUDIES:

The Preformulation studies are conducted to establish the physiochemical characteristics of the drug and its compatibility with the various excipients. The Preformulation studies are necessary to formulate drug into stable, safe and effective dosage form.

DRUG EXCIPIENT COMPATIBILITY STUDY[72]

The drug and the excipients chosen for the formulation were screened for compatibility by physical methods and Fourier Transform Infrared (FTIR) spectroscopic studies..

Compatibility study by FTIR

Infrared spectroscopy can be used to identify a compound and also to investigate the composition of the mixture. Pure drugs, polymers, excipients and drug excipient mixture were subjected to FTIR studies to investigate the Drug- excipient interactions. The IR spectra of the test samples were obtained by Pressed Pellet Technique using Potassium bromide.

Potassium bromide pellet method:

A small amount of finely ground solid samples intimately mixed with about 100times its weight of powdered potassium bromide. The finely ground mixture was then passed under very high pressure in a press (atleast 25,000 psig) to form a small pellet(about 1-2 mm thick and 1 cm in diameter). The resulting pellet was transparent to IR radiation and was run as such.

PREPARATION OF BUFFER SOLUTIONS

A. Preparation of 0.1N (pH 1.2) Hydrochloric Acid[64]

8.5ml of the hydrochloric acid was dissolved in water and made upto 1000 ml to get0.1N hydrochloric acid.

CALIBRATION CURVE[49,50]

For Nicorandil

100 mg of Nicorandil drug was transferred to a 100 ml standard flask and made upto volume with 0.1N HCl. 10 ml was pipetted out into separate 100 ml flask and made upto volume with 0.1N HCl. 2ml,4ml, 6ml,8ml and10ml were taken and made upto 100ml using 0.1N HCl. The absorbance of the resulting solutions was measured at 262nm using UV spectrophotometer. The Calibration curve was then plotted.

FORMULATION DEVELOPMENT[14,15,16]

Formulation of Nicorandil loaded Oil entrapped floating alginate beads

The Nicorandil loaded oil entrapped Floating Alginate beads was formulated by Emulsion Gelation method. In this method sodium alginate solution (2%w/v, 3%w/v, 4%w/v) containing floating polymer HPMC K100M(0.5% w/v) was prepared.Liquid paraffin in the concentration 15%v/v and 20% v/v was then added with high shear mixing. Nicorandil was then dispersed in the formed emulsion in fixed Drug: Alginate ratio(1:0.5, 1:1,1:2). This mixture was extruded, using syringe G 24 needle into 5% w/v calcium chloride solution. The gel beads were allowed to stand in solution for 30 minutes with mild stirring before being separated and dried. Floating Alginate beads were formulated by varying the Sodium Alginate concentration (2%w/v,3%w/v, 4% w/v) Drug:Polymer ratio(1:0.5,1:2,1:1) and oil concentration(15%v/v, 20% v/v).

FLOW CHART FOR FORMULATION OF NICORANDIL LOADED OIL ENTRAPPED FLOATING ALGINATE BEADS

EMULSION GELATION METHOD

Sodium Alginate + Distilled water

↓(Dissolve)

Add HPMC K 100M

↓

Add Liquid paraffin(Mineral oil)

↓**(**High shear mixing)

Drug is Dispersed

↓

Mixture Extruded using 24 gauge needle into 5% Calcium chloride solution

↓

Gel beads allowed to stand in solution for 30 minutes (curing time)

↓

Washed and Dried

↓(Optimized batch+ Magnesium stearate-5%)

Capsulated in a Hard gelatin capsule (20mg equivalent)

Table5: Formulation table for Nicorandil loaded oil entrapped floating alginate beads

Formula No.	Drug:Alginate ratio	Sodium alginate concentration %w/v	HPMC K100M %w/v	Mineral oil %v/v
1.	1:0.5	2	0.5	15
2.	1:0.5	2	0.5	20
3.	1:2	2	0.5	15
4.	1:2	2	0.5	20
5.	1:1	2	0.5	15
6.	1:1	2	0.5	20
7.	1:2	3	0.5	15
8.	1:2	3	0.5	20
9.	1:1	3	0.5	15
10.	1:1	3	0.5	20
11.	1:2	4	0.5	15
12.	1:2	4	0.5	20
13.	1:1	4	0.5	15
14.	1:1	4	0.5	20

EVALATION OF NICORANDIL LOADED OIL ENTRAPPED FLOATING ALGINATE BEADS

1. STUDY OF SIZE AND MORPHOLOGY OF BEADS[15,17]

The diameter of beads was determined by screw gauge. For this purpose, 20 dried beads were randomly selected from each batch and the mean diameter was determined by screw gauge. The least count of screw gauge was 0.005 mm. Surface and cross-sectional morphologies of beads were examined with a Scanning Electron Microscope.

2. PERCENTAGE YIELD

The percentage yield for the different formulations were calculated using the formula

Percentage yield = Practical yield / Theoritical yield × 100

3. DRUG LOADING(DL) AND ENTRAPMENT EFFICIENCY(EE)[16]

An accurately weighed sample of beads (100mg) was crushed in a mortar. The crushed material was dissolved in 75ml of 0.1N HCl, then made upto 100ml. This mixture was filtered and analyzed by UV/visible spectrophotometer at λ max 262 nm against 0.1N HCl as blank. The drug loading and entrapment efficiency percent can be calculated using the following equations.

DL% = (Actual drug content/ Weight of beads) × 100

EE% = (Actual drug content/ Theoretical drug content) × 100

4. DENSITY OF BEADS[16]

In this method floating beads were transferred to a measuring cylinder, tapped manually until constant volume was obtained. This volume is bulk volume(i.e.) it's the true volume of beads and the void space between them. The following equation was used to calculate the bulk density.

Bulk density = Mass of beads / Bulk volume

5. SWELLING STUDIES[15,30]

Beads were studied for swelling characteristics. Only those batches Were selected which have good drug content and entrapment efficiency more than 50%. Sample from drug-loaded beads were taken, weighed and placed in wire basket of USP Dissolution apparatus II. The basket containing beads was put in a beaker containing 100 ml of 0.1 N HCl (pH 1.2) maintained at 37^0C. The beads were periodically removed at predetermined intervals and weighed. Then the swelling ratio was calculated as per the following formula:

Swelling ratio = Weight of wet beads/ Weight of dried beads

6. ***IN-VITRO* FLOATING PROPERTIES[15,16]**

The Nicorandil loaded oil entrapped floating alginate beads were immersed in 900 ml of 0.1N HCl (pH 1.2) in USP type II apparatus at 50 rpm maintained at37 ± 5◦C . The floating ability (buoyancy) of beads was measured by visual observation. The time taken to float at the surface of dissolution medium (known as floating lag-time) and duration of floating were noted.

7. ***IN-VITRO*RELEASE STUDY[30,49,50]**

The dissolution rate of the prepared beads was studied using USP rotating paddle dissolution apparatus II. Known weight of beads containing equivalent amount of 20 mg of Nicorandil was placed in the dissolution medium (900 ml of buffer pH 1.2). The temperature was adjusted to 37 ±0.5 ^{0}C at 50 rpm. 5 ml of samples was withdrawn atspecified time intervals (1 hr) and replaced with fresh dissolution medium. The quantity of the drug released was determined using spectrophotometrically at 262 nm. The release rate of 20 mg of Nicorandil was determined.The experiment was carried out in triplicate and the average values of the released amount were calculated and plotted versus timeThe results were expressed as the percentage ofcumulative amount released as a functionof time.

PREFORMULATION STUDIES FOR CAPSULES:

FLOW PROPERTY MEASUREMENTS[64,73]

The flow properties of powers/beads are critical for an efficient Capsule filling operation. A good flow of the sample to be filled is necessary to assure efficient mixing and acceptable weight uniformity for the filled capsule. The flow property measurements include bulk density, tapped density, angle of repose, compressibility index and Hausner's ratio. The flow property measurements of the beads were determined.

a) BULK DENSITY (ρb)[73]

It is the ratio of total mass of beads to the bulk volume of beads. It was measured by pouring the weighed beads into a measuring cylinder and initial weight was noted. This initial volume was called the bulk volume. From this the bulk density was calculated according to the formula mentioned below. It is

expressed in g/ml and is given by

$$\rho b = M / Vb$$

Where, **M** and **Vb**are mass of powder and bulk volume of the beads respectively.

b) TAPPED DENSITY(ρt)[73]

It is the ratio of weight of the beads to the tapped volume of beads. The beads was introduced into a measuring cylinder with the aid of funnel and tapped for500 times on a wooden surface at a 2 sec interval and the volume attained is the tapped volume. It is expressed in g/ml and is given by

$$\rho t = M / Vt$$

Where, **M** and **Vt**are mass and tapped volume of the beads respectively.

c) ANGLE OF REPOSE (θ)[73]

The flow properties were characterized in terms of angle of repose, Carr's Index and Hausner's ratio. For determination of angle of repose (θ), the beads Were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The beads were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. Angle of repose was calculated using following equation.

$$\theta = \tan\text{-}1(h/r)$$

Where, **h** = height of pile in cm; **r** = radius of pile in cm

d)CARR'S INDEX (OR) % COMPRESSIBILITY[73]

It indicates beads flow properties. It was measured for determining the relative importance of interparticulate interactions. It is expressed in percentage and is given by

$$CI = \rho t - \rho b / \rho t X\ 100$$

Where, **ρt** and **ρb** are tapped density and bulk density respectively.

e) HAUSNER RATIO[73]

Hausner's ratio is an indirect index of ease of beads. It was calculated bythe following formula.

$$HR = \rho t / \rho b$$

Where, **ρt** and **ρb** are tapped density and bulk density respectively.

Table6: Angle of Repose, Compressibility Index and Hausner's Ratio[72]

Flow property	Angle of repose	Compressibility index	Hausner's ratio
Excellent	**25-30**	**<10**	1.00-1.11
Good	**31-35**	**11-15**	1.12-1.18
Fair	**36-40**	**16-20**	1.19-1.25
Passable	**41-45**	**21-25**	1.26-1.34
Poor	**46-55**	**26-31**	1.35-1.45
Very poor	**56-65**	**32-37**	1.46-1.59
Very very poor	**>65**	**>38**	>1.60

CAPSULATION OF THE OPTIMIZED NICORANDIL LOADED OIL ENTRAPPED FLOATING ALGINATE BEADS[14]

Nicorandil-loaded oil-entrapped beads equivalent to 20 mg of Nicorandil were mixed with magnesium stearate (5%, w/w) as lubricating agent for 3 minutes and filled into empty hard gelatin capsules (size 1) manually. Care wastaken to fill the contents completely to maintain the uniformity of contents and weight.

Table7: Formulation of capsules

Formula no.	Nicorandil beads (equivalent to 0.020 g)	Magnesium stearate (5%)
F-5	0.174g	0.0087g

EVALUATION OF CAPSULES

a) UNIFORMITY OF WEIGHT[64]

Intact capsules were weighed. The capsules were opened without losing any part of the shell and the contents were removed as completely as possible. The shell was washed with ether and the shell allowed to stand until the odour of the solvent was no longer detectable. The empty shell was weighed. The procedure was repeated with the remaining 19 capsules. Determine the average weight. Not more than two of the individual weights deviate from the average weight was determined.

Table 8: Uniformity of weight

S.No.	Average weight of capsule contents	Percentage deviation
1.	Less than 300mg	10
2.	300 mg or more	7.5

b) DISINTEGRATION[64]

Randomly six capsules were selected for disintegration test. Disintegration test was performed with disc in 0.1N HCl (37 ± 0.5^0C)using United States Pharmacopeia (USP) disintegration apparatus.

c) *IN-VITRO* DRUG RELEASE STUDIES[63,14]

The capsules containing Nicorandil loaded oil-entrapped beads were evaluated for their *in-vitro* drug release and were placed into900 ml of 0.1N HCl (pH 1.2), maintained at 37 ± 0.5◦Cand 50 rpm paddle speed in USP type-II dissolution apparatus. 5 ml of aliquots was collected at regular selected time intervals, and soon after same amount fresh buffer was replaced into dissolution vessel keeping the sink condition throughout the experiment. The collected aliquots were analyzed to find out the amount of drug release from the beads by using UV–visible spectrophotometer by measuring absorbance at λ_{max} of 262 nm.

***IN-VITRO* DRUG RELEASE STUDY OF MARKETED FORMULATION[64]**

The Nicorandil prolonged release marketed tablet was evaluated for its*in-vitro* drug release and were placed into900 ml of distilled water, maintained at 37 ± 0.5◦Cand 50 rpm paddle speed in USP type-II dissolution apparatus. 5 ml of aliquots was collected at regular selected time intervals, and soon after same amount fresh buffer was replaced into dissolution vessel keeping the sink condition throughout the experiment. The

collected aliquots were analyzed to find out the amount of drug release from the beads by using UV–visible spectrophotometer by measuring absorbance at $\lambda_{max}$of 262 nm.

EVALUATION OF *IN-VITRO* RELEASE KINETICS[14,74]

To study the *in-vitro* release kinetics of the optimized capsule containing Nicorandil loaded oil entrapped floating alginate beads, data obtained from dissolution study were plotted in various kinetics models.

1. Zero order equation

The zero order release can be obtained by plotting cumulative %
Percentage drug released vs. time in hours. It is ideal for the formulation to have release profile of zero order to achieve pharmacological prolonged action.

C=K0t

Where K0= Zero order constant

2. First order equation

The graph was plotted as log % cumulative drug remaining Vs time in hours.

Log C= log C0- Kt/2.303

Where C0= Initial concentration of drug

K= First order

t= Time in hours

3. Higuchi kinetics

The graph was plotted with % cumulative drug released Vs square root of time

Q = Kt ½

Where K= constant reflecting design variable system (differential rate constant)
t= Time in hours
The drug release rate is inversely proportional to the square root of time

4. Hixon and Crowell erosion equation

To evaluate the drug release with changes in the surface area and the diameter of particles, the data were plotted using the Hixon and Crowell rate equation.
The graph was plotted by cube root of % drug remaining vs. time in hours.

$$Q0^{1/3} - Qt^{1/3} = KHCXt$$

Where Qt= amount of drug released in time t.

Q0= Initial Amount of drug

KHC= Rate constant for Hixon Crowell equation

5. Korsmeyer-Peppas equation

To evaluate the mechanism of drug release, it was further plotted in Peppas equation as log cumulative % of drug released Vs log time.

$$Mt/M\alpha = Ktn$$

Where **Mt/Mα =** Fraction of drug released at time t

t = Release time

K= Kinetics constant (Incorporating structural and geometric characteristics of the formulation)

N= Diffusional exponent indicative of the mechanism of drug release

The present investigation was to formulate and evaluate Capsules containing Nicorandil loaded oil entrapped floating alginate beads for the treatment of Angina pectoris.

PREFORMULATION STUDIES

COMPATIBILITY STUDY

The possible interactions between the drug and the excipients used in theformulation were studied by FTIR spectroscopy. The results are given below

FTIR SPECTROSCOPY OF DRUG

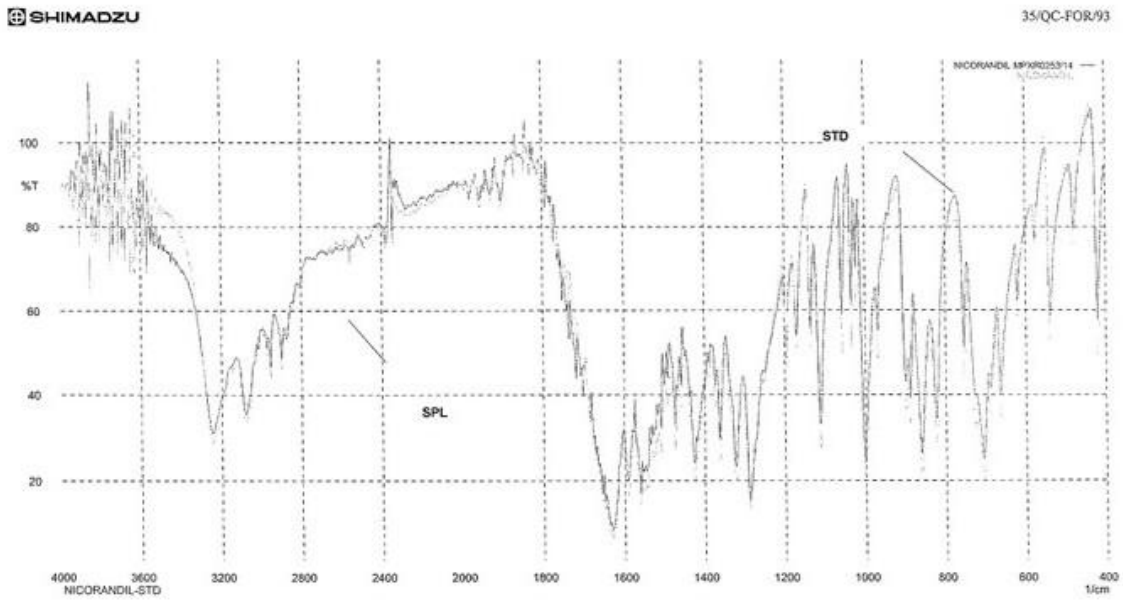


Fig.16 FTIR spectroscopy of Nicorandil

Table9: IR spectral interpretation of Nicorandil

Wave number(cm^{-1})	Type of vibration
1680	C=O stretching
3250	N – H stretching
3100	C – H (Aromatic)
1600-1400	C – N stretching (Pyridine)
1650	O - N stretching

FTIR SPECTROSCOPY OF NICORANDIL WITH EXCIPIENTS

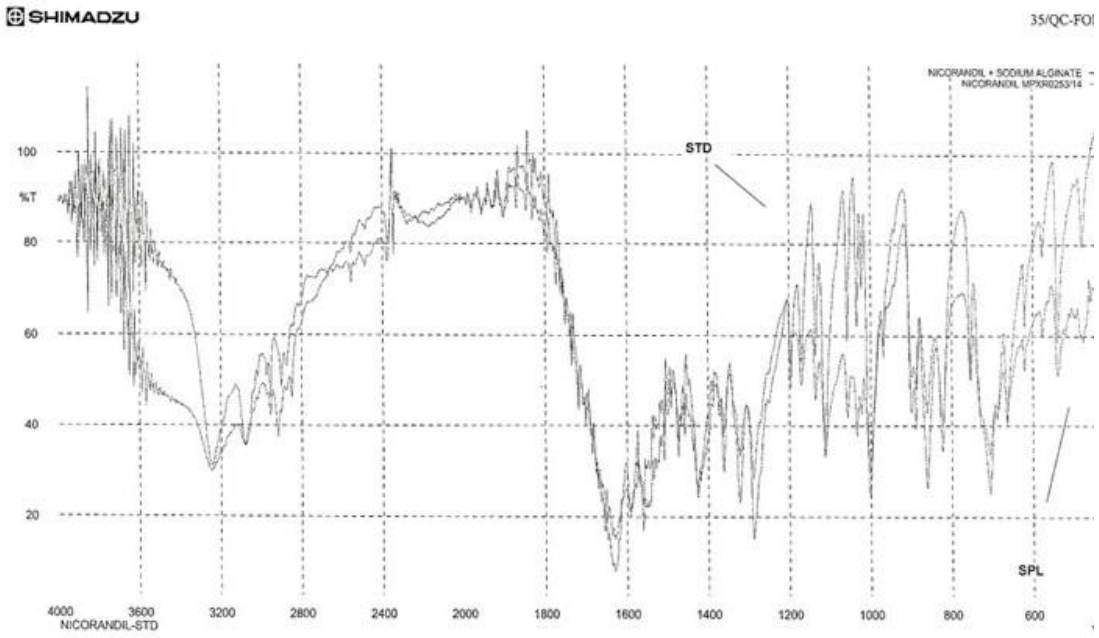


Fig.17 FTIR spectroscopy of Nicorandil with Sodium alginate

Table 10: IR spectral interpretation of Nicorandil with Sodium alginate

Wave number(cm^{-1})	Type of vibration
1680	C=O stretching
3250	N – H stretching
3100	C – H (Aromatic)
1600-1400	C – N stretching (Pyridine)
1650	O – N stretching

The results of IR spectra of active ingredient (Nicorandil) and sodium alginate revealed that therewas no considerable change observed in bands of Nicorandil.

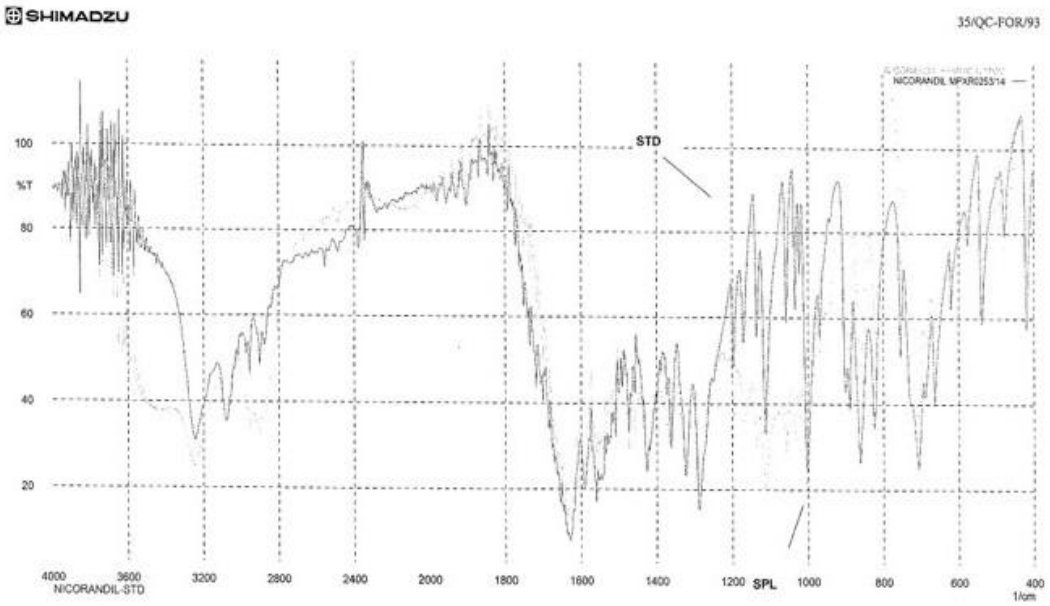


Fig.18 FTIR spectroscopy of Nicorandil with HPMC K 100 M

Table 11: IR spectral interpretation of Nicorandil with HPMC K 100 M

Wave number(cm^{-1})	Type of vibration
1680	C=O stretching
3250	N – H stretching
3100	C – H (Aromatic)
1600-1400	C – N stretching (Pyridine)
1650	O – N stretching

The results of IR spectra of active ingredient (Nicorandil) and HPMC K 100 M revealed that therewas no considerable change observed in the bands of Nicorandil.

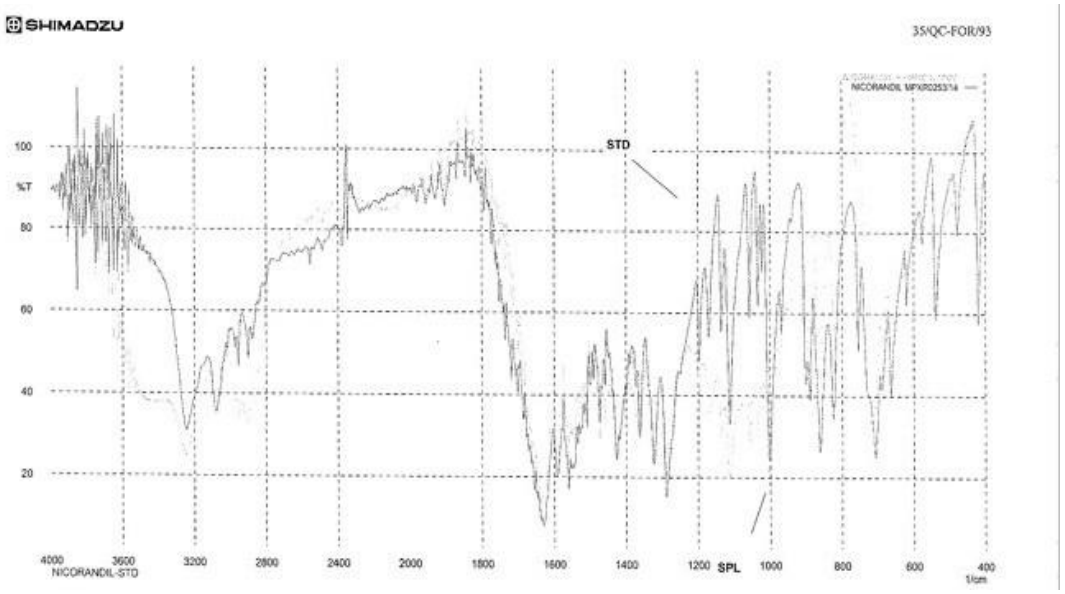


Fig.19 FTIR spectroscopy of Nicorandil with Magnesium stearate

Table 12: IR spectral interpretation of Nicorandil with Magnesium stearate

Wave number(cm^{-1})	**Type of vibration**
1680	C=O stretching
3250	N – H stretching
3100	C – H (Aromatic)
1600-1400	C – N stretching (Pyridine)
1650	O – N stretching

The results of IR spectra of active ingredient (Nicorandil) and Magnesium stearate revealed that therewas no considerable change observed in the bands of Nicorandil.

FTIR SPECTROSCOPY OF NICORANDIL WITH BLEND

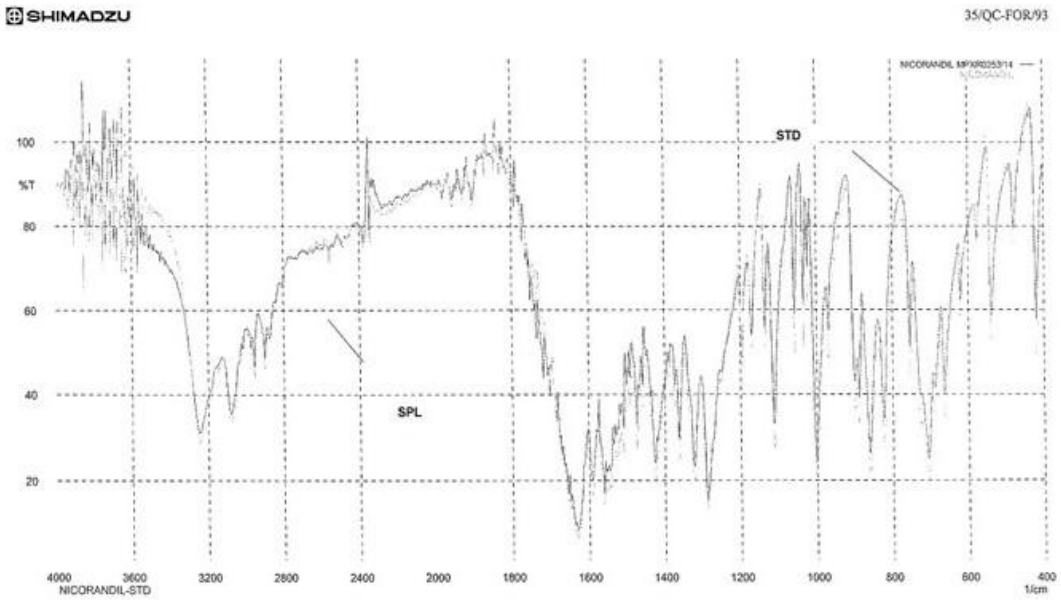


Fig.20 FTIR spectroscopy of Nicorandil with blend

Table 13: IR spectral interpretation of Nicorandil with blend

Wave number(cm^{-1})	Type of vibration
1680	C=O stretching
3250	N – H stretching
3100	C – H (Aromatic)
1600-1400	C – N stretching (Pyridine)
1650	O – N stretching

The results of IR spectra of active ingredient (Nicorandil) and the formulation blend revealed that there was no considerable change observed in the bands of Nicorandil. This shows the absence of anyinteraction between the drug and Excipients used in the formulation of Capsules containing Nicorandil loaded oil entrapped floating alginate beads.

CALIBRATION CURVE FOR NICORANDIL

The data for calibration curve of Nicorandil is given in table 14.

Table 14: Data for calibration curve of Nicorandil

CONCENTRATION (µg/ml)	ABSORBANCE
0	0
2	0.052±0.0029
4	0.108±0.0085
6	0.163 ±0.0136
8	0.217 ±0.0207
10	0.274 ±0.0191

R^2=0.999

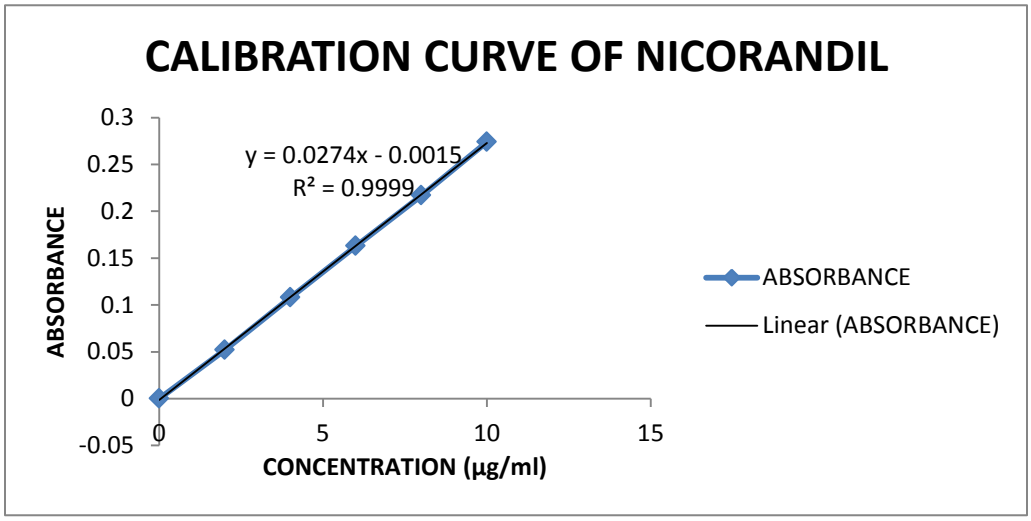


Fig.21 Calibration curve of Nicorandil

It was found that the solutions of Nicorandil in 0.1 N HCl show linearity (R2=0.999) in absorbance at concentrations of 2-10 µg/ml and obey beer Lambert's Law.[72]

EVALUATION OF NICORANDIL LOADED OIL ENTRAPPED FLOATING ALGINATE BEADS

PERCENTAGE YIELD

The Percentage yield of FAB of batches F-1 to F-14 are listed in Table 15.

Table 15:Percentage yield of FAB of batches F-1 to F-14

Formula No.	Percentage Yield %w/w
F-1	80.82
F-2	82.43
F-3	93.29
F-4	93.21
F-5	87.28
F-6	73.59
F-7	94.25
F-8	96.61
F-9	60.37
F-10	67.0
F-11	87.91
F-12	84.86
F-13	54.66
F-14	81.33

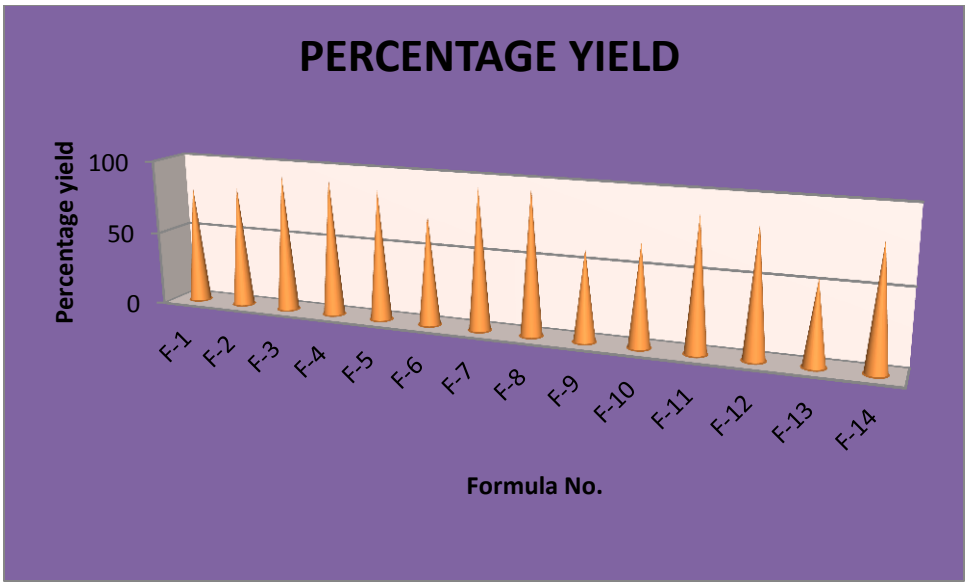


Fig. 22: Percentage yield of FAB of batches F-1 to F-14

STUDY OF SIZE AND MORPHOLOGY OF ALGINATE BEADS

MEAN DIAMETER

Table 16: Mean diameter of FAB of batches F-1 to F-14

Formula No.	Mean diameter (mm)±S.D. (n=20)
F-1	1.36±0.07
F-2	1.34 ±0.06
F-3	1.35 ±0.06
F-4	1.33 ±0.08
F-5	1.39 ±0.05
F-6	1.41 ±0.09
F-7	1.36 ±0.08
F-8	1.38 ±0.06
F-9	1.36 ±0.10

F-10	1.46 ±0.16
F-11	1.37 ±0.08
F-12	1.42 ±0.06
F-13	1.44 ±0.09
F-14	1.40 ±0.07

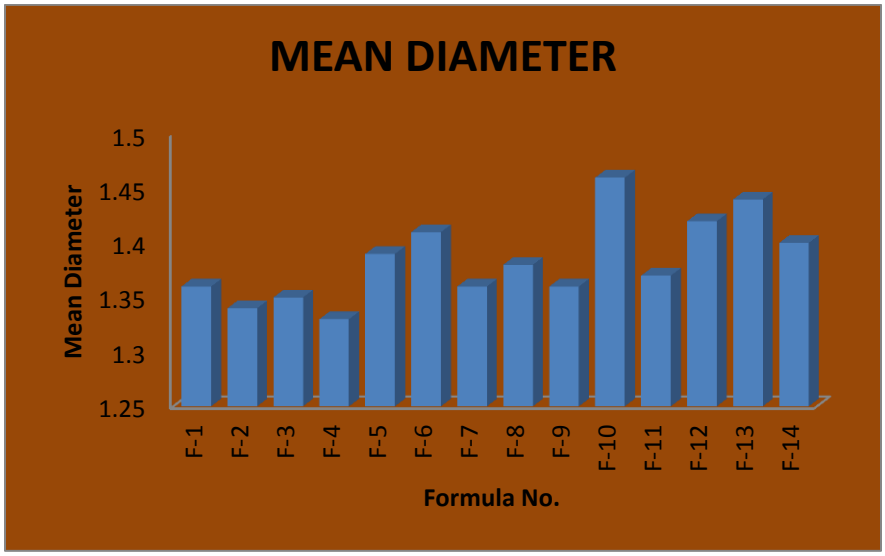


Fig.23:Mean diameter of FAB of batches F-1 to F-14

The mean diameter of FAB of batches F-1 to F-14 were found to be in the range of 1.33 to 1.44 mm as shown in table 16.

MORPHOLOGY OF FLOATING ALGINATE BEADS

The formulated FAB of batches F-1 to F-14 showed spherical geometry . The SEM photomicrograph of the entire bead structure and the cross-sectional view of the FAB of the optimized formulation F-5 shown in figures24 and 25 respectively reveals that the oil entrapped beads have an orange peel surface with corrugations where pores and channels are distributed throughout the surface.[16]

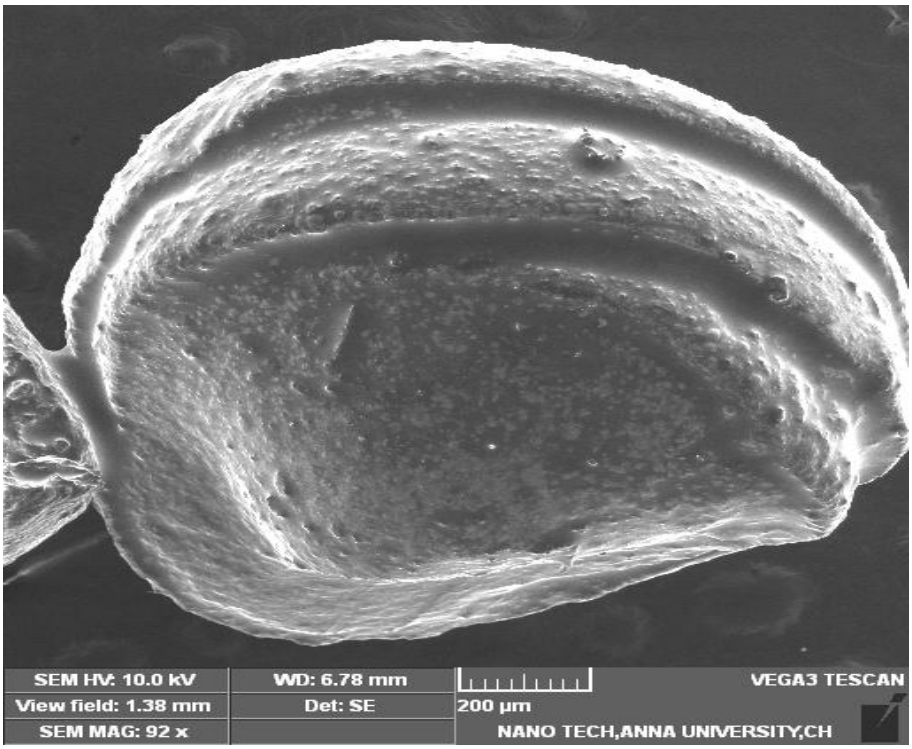


Fig.24SEM photomicrograph of FAB

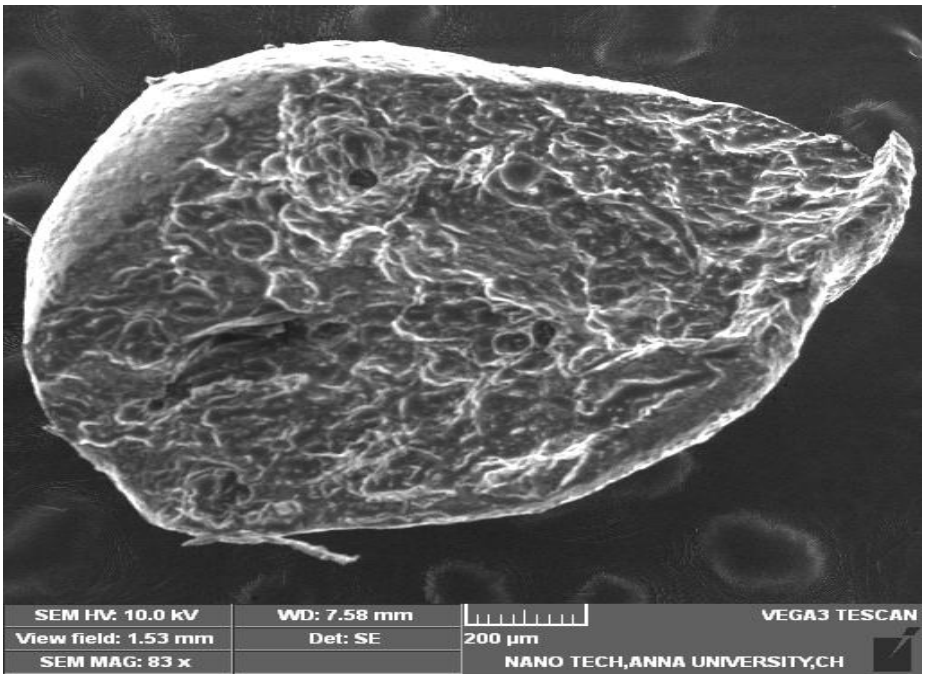


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Fig.25SEM photomicrograph of cross-sectional FAB

DENSITY

Table 17:Density of FAB of batches F-1 to F-14

Formula No.	Density g/ml
F-1	0.522
F-2	0.500
F-3	0.450
F-4	0.482
F-5	0.474
F-6	0.469
F-7	0.438
F-8	0.484
F-9	0.591
F-10	0.537
F-11	0.532
F-12	0.529
F-13	0.478
F-14	0.581

The bulk densities of various Nicorandil FAB formulas were found to be within the range (0.45-0.6g/ml) as shown in table 17, (i.e.) The density of all formulations obtained are less than the density of 0.1N HCl (1.004 g/ml).[16]Therefore the FAB float in 0.1 N HCl.

% ENTRAPMENT EFFICIENCY, % DRUG LOADING

Table 18: % Entrapment efficiency, % Drug loading of FAB of batches F-1 to F-14

Formula no.	% Entrapment efficiency (%w/w)	% Drug loading (%w/w)
F-1	78.72	16.23
F-2	80.03	13.5
F-3	87.59	5.85
F-4	90.93	4.39
F-5	93.04	10.69
F-6	97.89	9.02
F-7	82.77	6.83
F-8	87.96	5.85
F-9	69.84	9.09
F-10	74.50	9.52
F-11	83.61	8.60
F-12	86.18	7.20
F-13	66.80	10.69
F-14	71.93	11.19

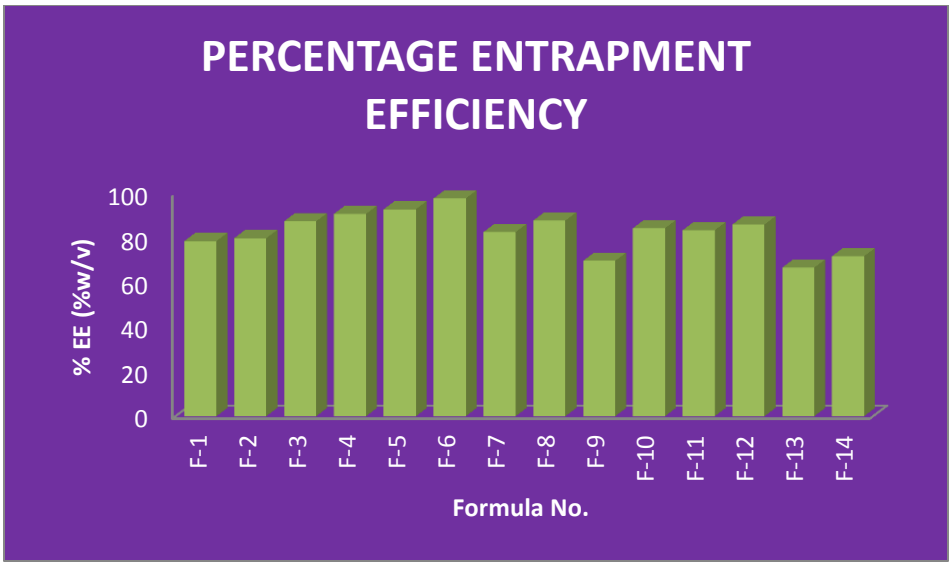

Fig.26: Percentage Entrapment efficiency of FAB of batches F-1to F-14

The % EE of the FAB ranged from 66.8 to 97.89%w/v. It was found that formulas prepared with 2%w/v sodium alginate solution had much higher EE% than those prepared with 3%w/v and 4%w/v. This may be due to the increased viscosity of the alginate solution to the extent that the formation of drops was strongly held up, where inability of calcium ions to penetrate the thick and viscous dispersions of this concentration may occur. The calcium ions ability to penetrate the dispersion reduced, cross linking decreased hence drug entrapped within the beads decreased. It was found that the %EE increased for the batches prepared with 20%w/v of oil concentration compared to 15%w/v. The barrier action of entrapped oil droplets protected the drug against diffusion to the surrounding medium during gelation process.[15,16]

IN-VITRO FLOATING PROPERTIES

Table 19: Floating lag time and Floating time of FAB of batches F-1 to F-14

Formula No.	Floating lag time (in seconds)	Floating time
F-1	2	>12 hours
F-2	4	>12 hours
F-3	2	>12 hours
F-4	3	>12 hours
F-5	2	>12 hours
F-6	2	>12 hours
F-7	5	>12 hours
F-8	3	>12 hours
F-9	4	>12 hours
F-10	2	>12 hours
F-11	3	>12 hours
F-12	3	>12 hours
F-13	6	>12 hours
F-14	2	>12 hours

All the batches had floating time greater than 12 hours. Thus had very less floating lag time (2 to 6 seconds) as given in Table 19. This is due to the lower relative density (0.86) of Light liquid paraffin which helped the beads to become buoyant.[15,16]

SWELLING RATIO

Table 20: Swelling ratio of FAB of batches F-1 to F-14

Time (hrs)	SWELLING RATIO													
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
1	1.63	1.62	1.59	1.56	1.61	1.57	1.26	1.21	1.35	1.29	0.95	0.87	1.14	1.05
2	1.67	1.65	1.61	1.58	1.63	1.60	1.29	1.24	1.39	1.33	1.05	0.91	1.18	1.08
3	1.61	1.59	1.58	1.53	1.59	1.58	1.27	1.20	1.37	1.28	0.98	0.88	1.15	1.05
4	1.58	1.55	1.53	1.47	1.55	1.54	1.23	1.17	1.34	1.26	0.92	0.85	1.12	1.03
5	1.56	1.51	1.48	1.44	1.50	1.49	1.18	1.15	1.32	1.26	0.89	0.82	1.09	1.00
6	1.56	1.49	1.44	1.39	1.48	1.45	1.15	1.13	1.29	1.24	0.88	0.81	1.07	0.99

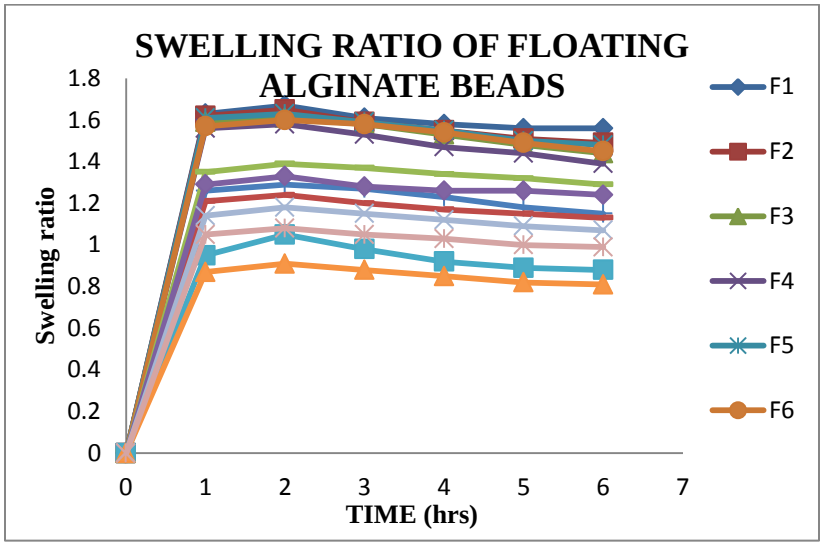

Fig. 27:Swelling ratio of FAB of batches F-1 to F-14

Swelling ratio of batches F-1 to F-14 for 6 hours is shown in the table 20. The polymer concentration has significant effect on swelling ratio of beads. As the amount of polymer and the oil concentration was increased, the swelling ratio of beads get decreased.[15]

IN-VITRO DRUG RELEASE STUDY

Table 21:*In-vitro* drug release study of FAB of batches F-1 to F-14

TIME (Hours)	CUMULATIVE PERCENTAGE DRUG RELEASE(%)													
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11	F-12	F-13	F-14
1	21.24	24.48	14.67	17.91	34.29	27.81	11.34	14.67	24.48	27.80	14.67	17.91	21.25	24.48
2	31.16	27.94	21.32	21.33	41.05	34.44	21.3	17.99	31.18	34.44	21.32	21.33	24.59	27.94
3	37.91	34.58	31.24	24.64	44.60	41.20	24.66	24.66	34.29	37.96	24.67	28.02	31.30	34.58
4	44.68	44.67	34.66	28.16	51.42	57.90	31.36	28.12	41.35	47.98	28.14	31.42	34.71	38.10
5	51.50	51.48	38.18	28.31	61.51	67.68	31.53	28.28	44.91	54.81	34.78	34.80	41.47	41.55
6	64.49	61.57	41.85	34.95	68.42	68.05	34.95	34.91	51.73	61.68	38.30	41.59	45.03	48.34
7	78.33	71.72	45.18	38.47	75.36	75.00	41.71	45.00	58.58	65.35	41.74	45.15	48.51	55.18
8	88.65	85.25	45.43	45.25	85.58	82.42	48.50	48.49	68.71	72.18	45.30	45.39	55.35	62.05
9	98.95	98.86	48.91	48.73	89.37	88.99	52.10	48.75	75.65	82.48	52.12	48.88	58.98	67.14
10			52.13	52.33	89.86	92.71	55.62	58.91	79.73	86.16	55.64	52.75	65.87	79.14
11			62.60	59.18	96.90	99.79	62.49	62.45	83.06	89.96	59.27	55.99	76.03	82.89
12			69.07	66.07	104.24	113.46	66.16	69.38	90.07	93.68	62.83	62.86	83.30	86.58

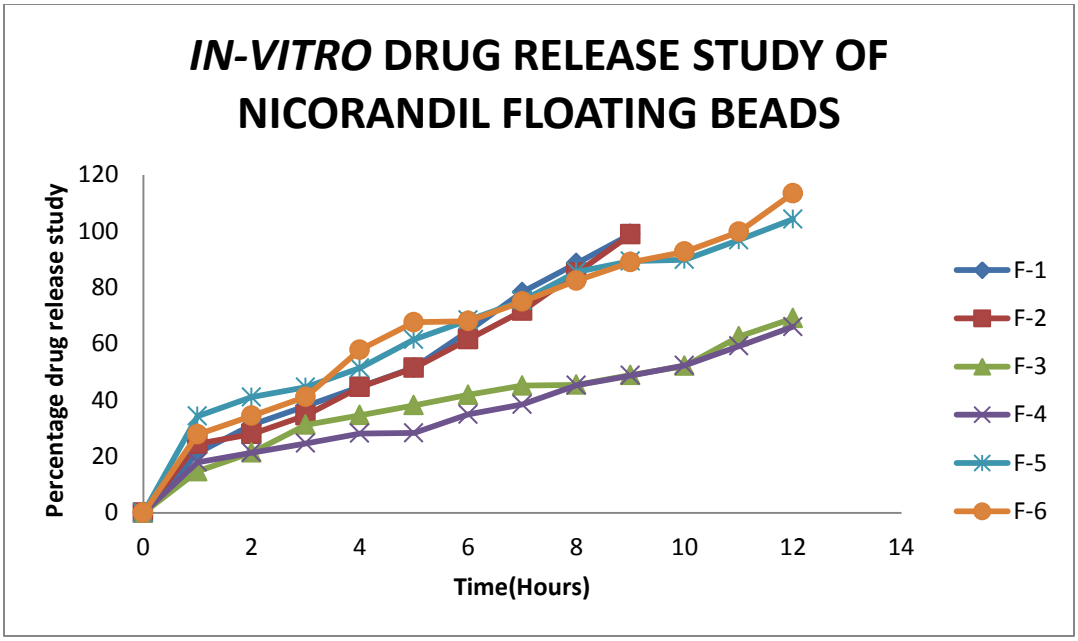

Fig.28:*in-vitro* drug release study of FAB of batches F-1 to F-6

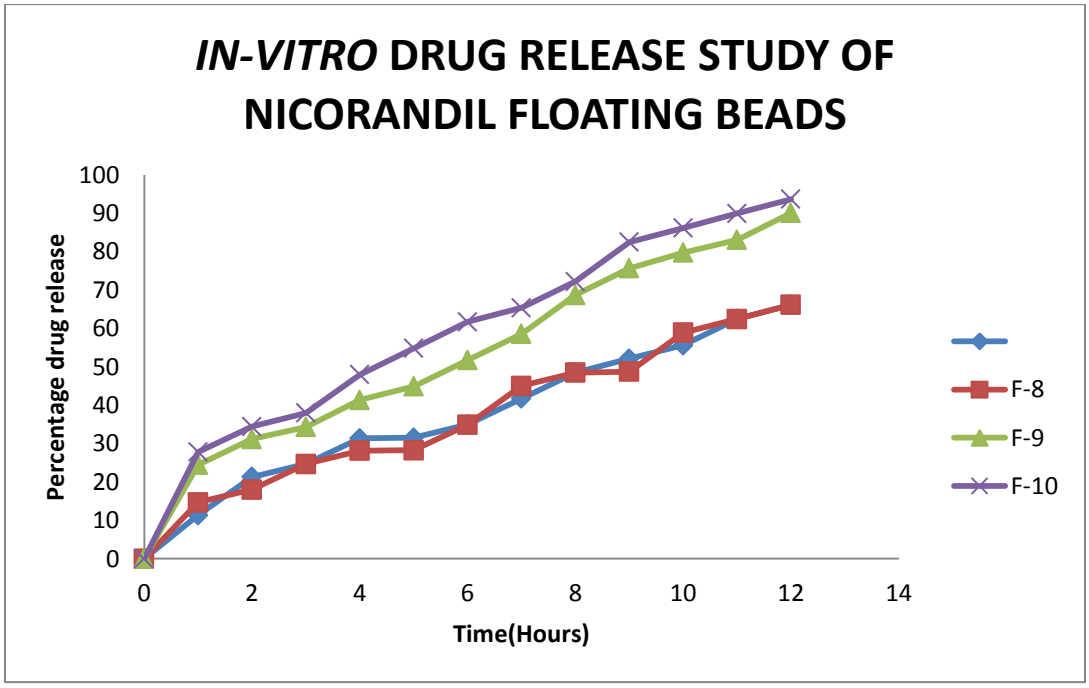

Fig. 29:*in-vitro* drug release study of FAB of batches F-7to F-10

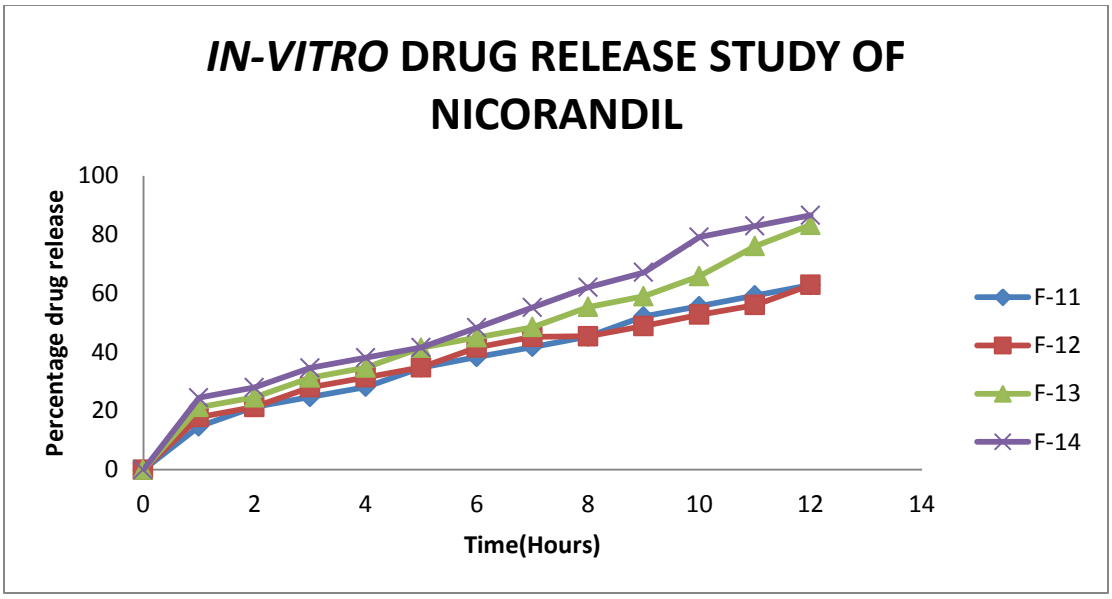

Fig. 30: *in-vitro* drug release study of FAB of batches F-11 to F-14

The drug release study of batches F-1 to F-14 were carried out and the percentage drug release from the FAB ranged from 66.16 to 113.46 at the end of 12 hours. The results showed that the drug release pattern was affected by polymer concentration, ratio of drug polymer mixture. All the batches showed the initial burst release. This may be due to the water-soluble nature of the drug. It may also be possible that the drug particles were dragged on the surface of the beads during curing in aqueous surrounding medium, which resulted in initial burst release. The results indicate that the drug release slows down with increasing polymer concentration. The batch which showed optimum drug release at the end of 12 hours was selected as the optimized formulation and it was found to be F-5. The percentage drug release was 104.24 %. My results corresponds to earlier reports.[15,16]

PREFORMULATION STUDIES OF CAPSULES

FLOW PROPERTY MEASUREMENTS

Table 22: Flow property measurements of FAB of the optimized batch F-5

S.NO.	Parameters	Results	Inference
1.	Bulk density	0.425±0.007	-
2.	Tapped density	0.4316± 0.0043	-
3.	Angle of Repose	18^0 51'± 1.48	Excellent
4.	Carr's index	2.13± 0.0711	Excellent
5.	Hausner's ratio	1.021 ±0.00047	Excellent

The results showed that the prepared FAB possess excellent flow property so the use of glidant is not required.

EVALUATION OF CAPSULES

The disintegration time of the empty capsule was found to be 12 minutes. This complies with the official standard.

Table 23: Uniformity of weight of the optimized batch F-5

S.No.	Parameters	Results
1.	Uniformity of weight*	0.1830±0.0004

*Mean±SD(n=20)

The capsules had uniformity of weight. The result complies with the standard.

IN-VITRO DRUG RELEASE STUDY OF OPTIMIZED AND MARKETED FORMULATION

Table 24: Comparison table of *in-vitro* drug release study of optimized and marketed formulation

Time(Hours)	F-5*	Marketed Formulation*
1	29.43±1.62	29.35±0.001
2	37.73± 3.27	32.93±0.001
3	44.51 ±3.29	37.24±0.9
4	51.33 ±3.31	44.20± 2.48
5	58.18 ±3.33	46.99±1.71
6	63.45 ±1.6	51.44±2.51
7	71.17 ±4.04	57.63 ±1.69
8	80.56 ±1.7	64.59 ±1.62
9	87.55 ±1.64	72.36 ±0.56
10	91.32 ±1.58	77.89±5.7
11	93.58 ±3.26	84.31 ±6.75
12	98.88 ±1.61	97.4 ±0.78

* MEAN±SD(n=2)

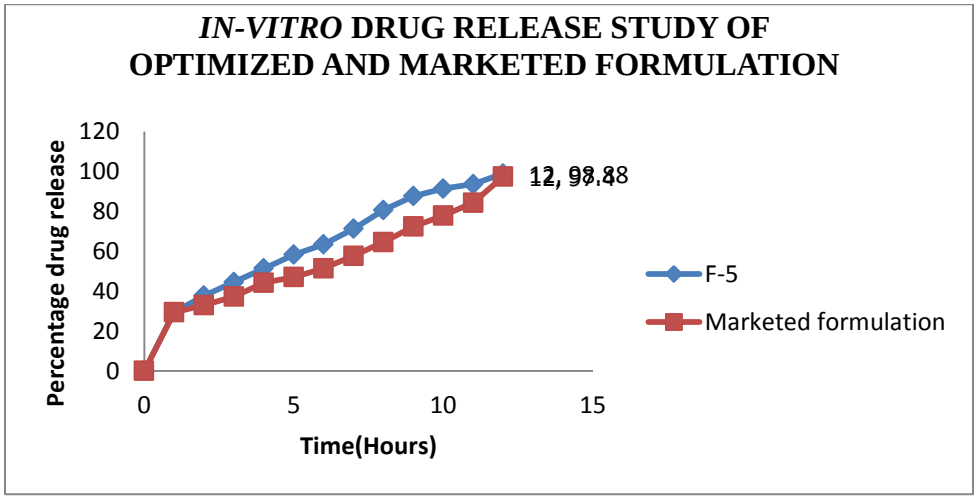

Fig. 31: *in-vitro* drug release study of the optimized and marketed formulation

The *in-vitro* drug release study of the optimized and marketed formulation showed that the drug release pattern of the capsule containing optimized formulation was similar to that of the marketed formulation.

IN-VITRO RELEASE KINETICS[14,15]

The values obtained from *in-vitro* dissolution of the capsules containing Nicorandil loaded oil entrapped floating alginate beads were fitted in various kinetic models. The results are given in table 25 and figures 32-36.

Table 25:*in-vitro* release kinetics of the optimized batch F-5

Time (Hours)	Log time (Hours)	Sq. Root of time (Hours)	Cum % drug release	Cum % drug remaining	Log cum % drug release	Log cum % drug remaining	Cube root of cum % drug remaining
0	∞	0	0	100	∞	2	4.64
1	0	1	29.43	70.57	1.46	1.84	4.13
2	0.30	1.41	37.73	62.27	1.57	1.79	3.96
3	0.47	1.73	44.51	55.49	1.64	1.74	3.81
4	0.60	2	51.33	48.67	1.71	1.68	3.65
5	0.69	2.23	58.18	41.82	1.76	1.62	3.47
6	0.77	2.44	63.45	36.55	1.80	1.56	3.31
7	0.84	2.64	71.17	28.83	1.85	1.45	3.04
8	0.90	2.82	80.56	19.44	1.90	1.28	2.68
9	0.95	3	87.55	12.45	1.94	1.09	2.31
10	1	3.16	91.32	8.68	1.96	0.93	2.05
11	1.04	3.31	93.48	6.52	1.97	0.81	1.86
12	1.07	3.46	98.88	1.12	1.99	0.04	1.03

ZERO ORDER KINETICS

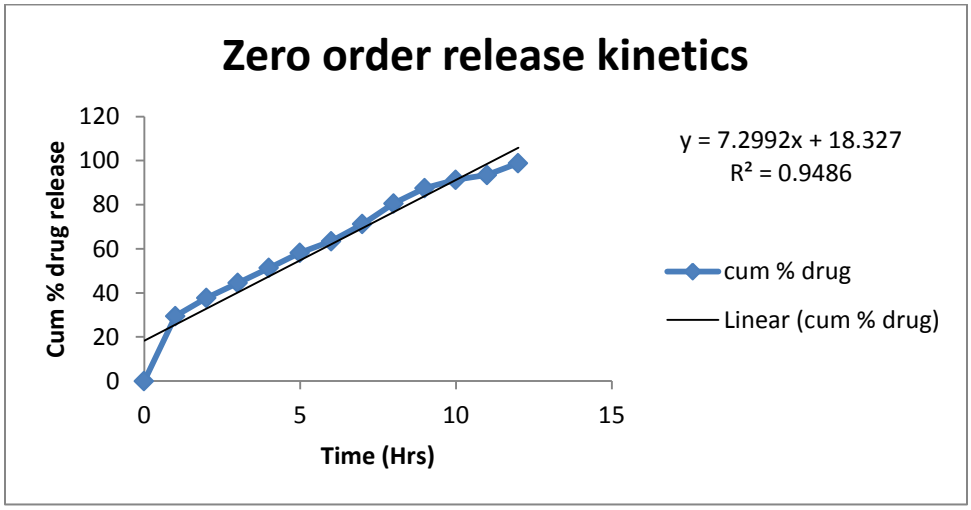

Fig. 32:Zero order release kinetics

FIRST ORDER KINETICS

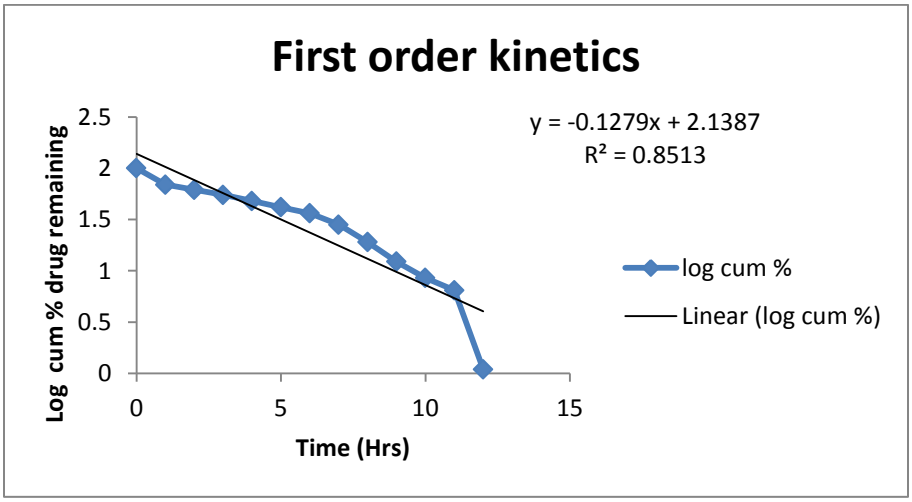

Fig.33:First order kinetics

HIGUCHI RELEASE KINETICS

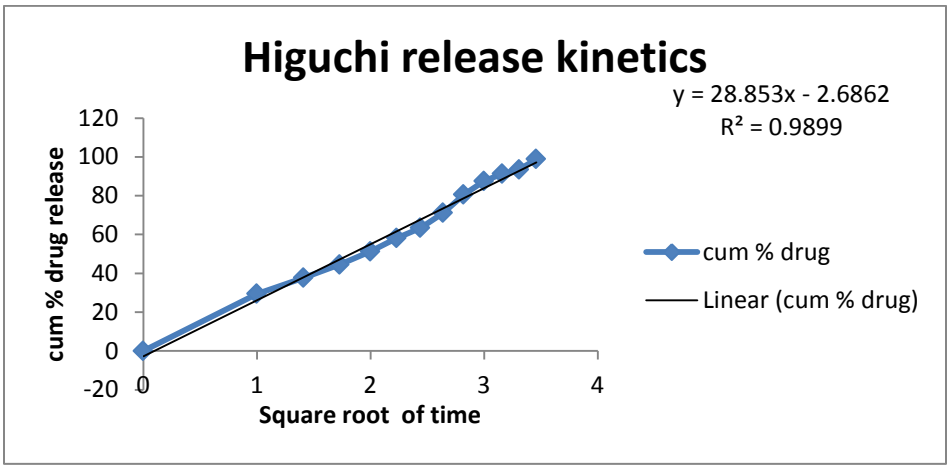

Fig. 34:Higuchi release kinetics

KORSMEYER-PEPPAS KINETICS

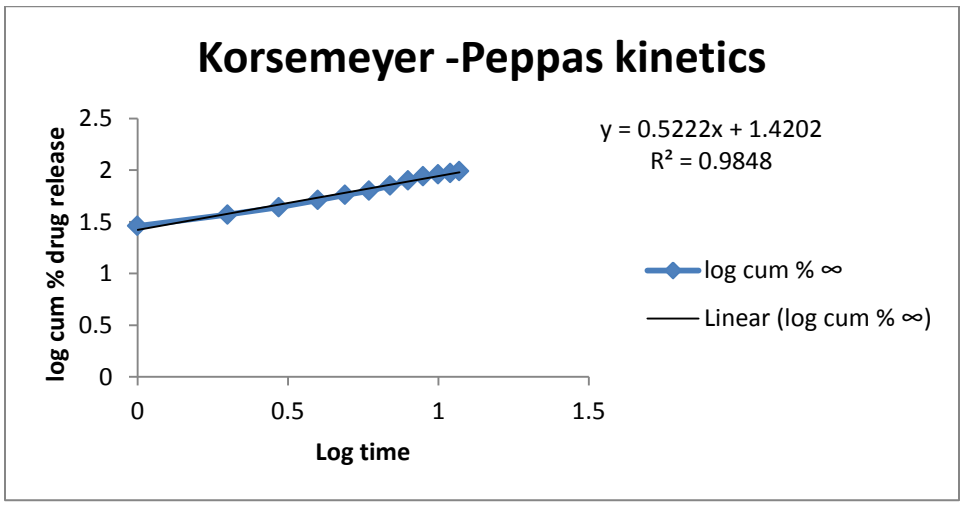

Fig. 35:Korsemeyer -Peppas kinetics

HIXON-CROWELL KINETICS

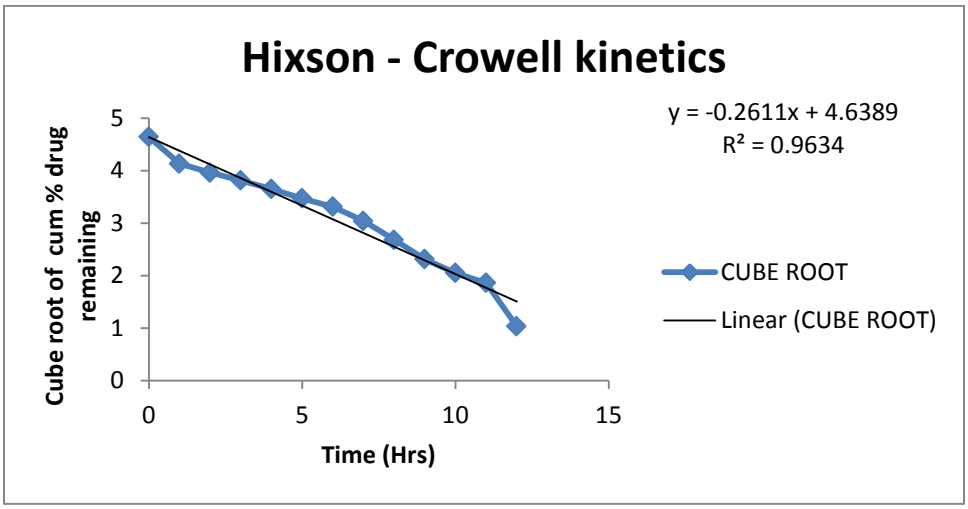

Fig. 36: Hixson - Crowell kinetics

DETERMINATION OF RELEASE KINETICS OF OPTIMIZED FORMULATION

- After studying the different kinetics models, it could be concluded that release of Nicorandil from batch F-5 followed the Higuchi model i.e. square root kinetics in which R^2 value was 0.989. Thus the release from these batches was diffusion controlled.
- The n value of Korsmeyer- Peppas equation was found to be 0.522, from that it was concluded that the release followed non- fickian transport.

- The present study was aimed to develop Capsules containing Nicorandil loaded oil entrapped floating alginate beads by varying sodium alginate concentration viz 2,3 and 4%w/v, Drug:Alginate ratio viz 1:0.5, 1:2,1:1 and oil (Liquid paraffin) concentration viz 15%v/v and 20%v/v.

- Chemical compatibility study was performed using FTIR spectroscopy and FTIR studies revealed that there was no change in major peaks thus confirming no interaction between the drug and excipients.

- Nicorandil loaded floating alginate beads was prepared by Emulsion Gelation method using sodium alginate, HPMC K100M, Liquid paraffin.

- The formulated FAB were evaluated for Percentage yield, Size and Morphology, %Entrapment efficiency, %Drug loading, Density, *in-vitro* floating properties, *in-vitro* drug release studies.

- Based on the *in-vitro* drug release studies, the optimized formulation was selected and it was found to be F-5.

- The preformulation studies were carried out for the optimized formulation F-5 to determine the flow property of the FAB. The results revealed that the beads possess excellent flow property. Nicorandil-loaded oil-entrapped beads equivalent to 20 mg of Nicorandil equivalent weight were mixed with magnesium stearate (5%, w/w) as lubricating agent for additional 3 min and filled into empty hard gelatin capsule.

- The formulated capsules were evaluated for uniformity of weight, Disintegration time and *in-vitro* drug release study. The formulated capsules were found to be within the limit in case of uniformity of weight.

- The capsule containing Nicorandil loaded floating alginate beads was compared with the Marketed prolonged release formulation. The results showed excellent similarity.

- The release kinetics of the capsule containing the optimized Nicorandil loaded oil entrapped FAB showed that it follows Higuchi release kinetics. The release of the drug from the dosage form is carried out by diffusion and follows Korsmeyer peppas kinetics and the n value is greater than 0.5 indicating non-Fickian release.

- The floating beads have been employed to make a sustained release of the drug in the stomach to enhance bioavailability and to decrease dose dumping and hence overcome its side effects.

- The developed formulation shows an alternative to the conventional dosage form for the treatment of Angina pectoris in patients.

FUTURE PLAN

- Scale up studies of the optimized formulation.

- *In-vivo* studies and *in vivo- in vitro* correlation studies.

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